SPECIFICATION

DRUGS CONTAINING CHYMASE INHIBITORS AS ACTIVE INGREDIENTS

TECHNICAL FIELD

The present invention relates to drugs that contain chymase inhibitors as active ingredients, wherein the drugs are agents for improving glucose intolerance or for preventing and/or treating diseases caused by glucose intolerance.

More specifically, the present invention relates to the drugs for diseases caused by glucose intolerance, wherein the diseases are diabetes and/or diabetes complications, wherein the diabetes complications are diabetic nephropathy, diabetic retinopathy, diabetic peripheral neuropathy, hyperinsulinism, insulin resistance syndrome, arteriosclerosis, acute coronary syndrome, arteriosclerosis obliterans, angitis, stroke, hypertension, nephropathy, nephritis, renal artery aneurysm, renal infarction, or obesity.

BACKGROUND ART

Glucose intolerance refers to insufficiency of insulin secretion response due to glucose load and/or reduction of insulin action in skeletal muscles or adipose tissues. In many cases, glucose intolerance is caused by insulin resistance. Glucose intolerance is regarded as conditions that precede the onset of diabetes and is multiply associated with various metabolic diseases (obesity, hypertension, hypertriglyceridemia and the like). This multiple metabolic disorder is also referred to as the deadly quartet ("The deadly quartet. Upper-body obesity, glucose intolerance, hyper triglyceridemia, and hypertension." Archives of International Medicine, (USA) 1989, Vol. 149, No. 7, p. 1514), insulin resistance syndrome ("Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease." Diabetes Care, (USA) 1991, Vol. 14, No. 3, p. 173), or multiple risk factor syndrome. Insulin intolerance also enhances occurrence frequency of coronary artery diseases such as angina pectoris, myocardial infarction and stroke.

Continuous glucose intolerant conditions induce new onset of diabetes and also enhances its progress. Therefore, improvement of glucose intolerance is considered effective in preventing onset of diabetes, inhibiting its progress and preventing onset of diabetes complications.

Diabetes is a disease that causes increase in the blood glucose level before or after meals. Two types of diabetes are known: type I diabetes that significantly reduces insulin secretion from pancreas and type II diabetes that causes insulin resistance in liver, skeletal muscles, or adipose tissues and deficiency of insulin secretion by pancreas due to an excessive intake of food, insufficient exercise and the like. Most of diabetics belong to type II diabetics.

Diabetes, as it progresses, induces complications such as diabetic retinopathy, diabetic nephropathy and diabetic peripheral neuropathy, and furthermore causes various serious diseases such as renal insufficiency, arteriosclerosis and hypertension. Accordingly prevention and treatment of diabetes is important for prevention of diabetes complications.

Treatment of glucose intolerance and/or diabetes widely uses, in addition to dietetic treatment and kinesitherapy, blood glucose level controlling drugs such as sulfonylureas, biguanides, α-glycosidase inhibitors and agonists for peroxisome proliferation-related receptor γ, or other various therapeutic agents. Either of the treatments is, however, not yet satisfactory with respect to effectiveness, patients' compliance, side effects, etc. In fact, the number of diabetics and that of potential diabetics tend to increase in these years. There is still a demand for therapeutic agents with high effectiveness and insignificant side effects.

Chymase is one of neutral proteases occurring in mast cell granules and is deeply involved in various biological reactions related to mast cells. There has been reported various actions of chymase, for example, enhancement of degranulation in mast cells, activation of interleukin-1β (IL-1β), activation of matrix protease, degradation of fibronectins and type IV collagen, enhancement of release of transforming growth factor-β (TGF-β), activation of substance P and vasoactive intestinal polypeptide (VIP), conversion of angiotensin (Ang)I into AngII, conversion of endothelin and the like.

With respect to the relationship between mast cells containing chymase and glucose metabolism, however, there have been few reports so far, and a number of questions remain

unresolved. Some study reported that mast cells are scarcely present in pancreas or kidney ("Mast cell distribution in rats" Arzneimittelforschung, (Germany) 1994, Vol. 44, No. 3, p. 370). Further, nothing has been reported on the relationship between β cells in Langerhans island and mast cells or on involvement of chymase in insulin secretion in pancreas.

DISCLOSURE OF THE INVENTION

An object of the present invention is to provide drugs that contain chymase inhibitors as active ingredients, wherein the drugs are agents for improving glucose intolerance or for preventing and/or treating diseases caused by glucose intolerance such as diabetes and/or diabetes complications.

The present investors found that chymase inhibitors improve glucose intolerance and achieved the present invention.

In other words, the present invention is drugs that contain chymase inhibitors as active ingredients, wherein the drugs are agents for improving glucose intolerance or for preventing and/or treating diseases caused by glucose intolerance.

Furthermore, the present invention is the preventive agents and/or therapeutic agents for diseases caused by glucose intolerance, wherein the diseases are diabetes and/or diabetes complications, wherein the diabetes complications are diabetic nephropathy, diabetic retinopathy, diabetic peripheral neuropathy, hyperinsulinism, insulin resistance syndrome, arteriosclerosis, acute coronary syndrome, arteriosclerosis obliterans, angitis, stroke, hypertension, renal insufficiency, nephropathy, nephritis, renal artery aneurysm, renal infarction or obesity.

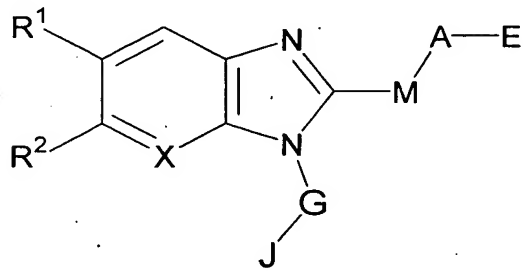
BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing the blood glucose levels for Wild, TGM and TGM/ChI after glucose loading. Fig. 2 is a graph showing the concentrations of blood insulin for Wild, TGM and TGM/ChI after glucose loading.

BEST MODE FOR CARRYING OUT THE INVENTION

Drugs in the present invention use chymase inhibitors as active ingredients. The diseases caused by glucose intolerance related to the present invention include diabetes and/or diabetes complications. The diabetes complications include diabetic nephropathy, diabetic retinopathy, diabetic peripheral neuropathy, hyperinsulinism, insulin resistance syndrome, arteriosclerosis, acute coronary syndrome, arteriosclerosis obliterans, angitis, stroke, hypertension, renal insufficiency, nephropathy, nephritis, renal artery aneurysm, renal infarction, obesity and the like.

Chymase inhibitors used in the present invention are, although not particularly limited, preferably the benzimidazole derivatives or medically acceptable salts thereof described in WO 01/53291, WO 01/53272 and WO 00/03997. In particular, preferred is the following compound (I):



(I)

[wherein R^1 and R^2 simultaneously or each independently represent hydrogen, halogen, trihalomethyl, cyano, hydroxyl, C_1–C_4 alkyl or C_1–C_4 alkoxy, or R^1 and R^2 taken together represent –O–CH_2–O–, –O–CH_2CH_2–O– or –$CH_2CH_2CH_2$– (wherein the carbon atoms may be optionally substituted with one or more C_1–C_4 alkyl);

A represents substituted or unsubstituted straight, cyclic or branched C_1–C_7 alkylene or C_1–C_7 alkenylene, which may be interrupted by one or more of atoms or groups selected from –O–, –S–, –SO_2– and –NR^3–, (wherein R^3 represents hydrogen or straight or branched C_1–C_6 alkyl). The substituents on these groups are selected from halogen, hydroxyl, nitro, cyano, straight or branched C_1–C_6 alkyl, straight or branched C_1–C_6 alkoxy (including cases wherein the neighboring two form an acetal), straight or branched C_1–C_6 alkylthio, straight or branched C_1–C_6 alkylsulfonyl, straight or branched C_1–C_6 acyl, straight or branched C_1–C_6 acylamino, trihalomethyl, trihalomethoxy, phenyl, oxo or phenoxy optionally substituted with one or more

halogen atoms. These substituents may be present each independently at one or more arbitrary positions in the alkylene or alkenylene, except for the case wherein M represents a single bond and the carbon atom of A directly bonded to M is substituted with a hydroxyl and a phenyl at the same time;

E represents $-COOR^3$, $-SO_3R^3$, $-CONHR^3$, $-SO_2NHR^3$, tetrazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl or 5-oxo-1,2,4-thaidiazol-3-yl, (wherein R^3 is as defined above);

G represents substituted or unsubstituted straight or branched C_1–C_6 alkylene, which may be interrupted by one or more of atoms or groups selected from –O–, –S–, $-SO_2-$ and $-NR^3-$, (wherein R^3 is as defined above, provided that either of these atoms or groups is not directly bonded to the benzimidazole ring). The substituents on the alkylene are selected from halogen, hydroxyl, nitro, cyano, straight or branched C_1–C_6 alkyl, straight or branched C_1–C_6 alkoxy (including cases wherein neighboring two form an acetal), trihalomethyl, trihalomethoxy, phenyl or oxo;

M represents a single bond or $-S(O)_m-$, wherein m is an integer ranging from 0 to 2;

J represents substituted or unsubstituted C_4–C_{10} heteroaryl (one or more heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur in the ring), except for imidazole or unsubstituted pyridine ring. The substituents on the heteroaryl are selected from halogen, hydroxyl, nitro, cyano, straight or branched C_1–C_6 alkyl, straight or branched C_1–C_6 alkoxy (including cases wherein neighboring two form an acetal), straight or branched C_1–C_6 alkylthio, straight or branched C_1–C_6 alkylsulfonyl, straight or branched C_1–C_6 acyl, straight or branched C_1–C_6 acylamino, substituted or unsubstituted anilido, trihalomethyl, trihalomethoxy, phenyl, oxo, $COOR^3$ and phenoxy optionally substituted with one or more halogen atoms. One or more of these substituents each may be present at any positions in the ring; and

X represents –CH= or nitrogen.]

The substituents in the compounds of formula (I) in the present invention are as follows:

R^1 and R^2 simultaneously or each independently represent hydrogen, halogen, trihalomethyl, cyano, hydroxyl, C_1–C_4 alkyl or C_1–C_4 alkoxy, or R^1 and R^2 taken together represent $-O-CH_2-O-$, $-O-CH_2CH_2-O-$ or $-CH_2CH_2CH_2-$, wherein the carbon atoms may be

optionally substituted with one or more C_1–C_4 alkyl.

The C_1–C_4 alkyl of R^1 and R^2 includes specifically methyl, ethyl, (n-, i-)propyl and (n-, i-, s-, t-)butyl, and is preferably methyl. The C_1–C_4 alkoxy includes specifically methoxy, ethoxy, (n-, i-)propyloxy and (n-, i-, s-, t-)butyloxy.

Groups suitable to R^1 and R^2 include hydrogen, halogen, trihalomethyl, cyano, hydroxyl, C_1–C_4 alkyl and C_1–C_4 alkoxy. R^1 and R^2 are preferably hydrogen, halogen, trihalomethyl, cyano, C_1–C_4 alkyl or C_1–C_4 alkoxy, more preferably hydrogen, C_1–C_4 alkyl, C_1–C_4 alkoxy, halogen or cyano, further preferably hydrogen, Cl, F, trifluoromethyl, methyl, methoxy or ethoxy, further more preferably hydrogen, C_1–C_4 alkyl, or C_1–C_4 alkoxy, and especially preferably hydrogen, methyl or methoxy.

A represents substituted or unsubstituted straight, cyclic or branched C_1–C_7 alkylene or alkenylene. The unsubstituted straight, cyclic or branched C_1–C_7 alkylene includes methylene, ethylene, (n-, i-)propylene, 2,2-dimethylpropylene, (n-, i-, t-)butylene, 1,1-dimethylbutylene, n-pentylene, cyclohexylene and the like. It is preferably ethylene, n-propylene, 2,2-dimethylpropylene, or (n-, t-)butylene, more preferably n-propylene or 2,2-dimethylpropylene, and especially preferably, n-propylene. The unsubstituted straight or branched C_1–C_7 alkenylene includes vinylene, propenylene, butenylene, pentenylene and the like.

These alkylene or alkenylene may be interrupted by one or more of atoms or groups selected from –O–, –S–, $–SO_2–$ and $–NR^3–$, (wherein R^3 represents hydrogen or straight or branched C_1–C_6 alkyl), provided that either of these atoms or groups is not directly bonded to M. An example is ethylene, n-propylene, or (n-, t-)butylene interrupted by these atoms or groups. Further specifically it is $–CH_2OCH_2–$, $–CH_2OCH_2CH_2–$, $–CH_2SCH_2–$, $–CH_2SCH_2CH_2–$, $–CH_2SO_2CH_2–$, $–CH_2SO_2CH_2CH_2–$, $–CH_2NR^4CH_2–$, $–CH_2NR^4CH_2CH_2–$ or the like, and preferably $–CH_2OCH_2–$, $–CH_2SCH_2–$ or $–CH_2SO_2CH_2–$.

The substituents on these alkylene are selected from halogen, hydroxyl, nitro, cyano, straight or branched C_1–C_6 alkyl, straight or branched C_1–C_6 alkoxy (including cases wherein neighboring two form an acetal), straight or branched C_1–C_6 alkylthio, straight or branched C_1–C_6 alkylsulfonyl, straight or branched C_1–C_6 acyl, straight or branched C_1–C_6 acylamino,

trihalomethyl, trihalomethoxy, phenyl, oxo and phenoxy optionally substituted with one or more halogen atoms. One or more of these substituents each may independently be present at any positions in the alkylene or alkenylene, except for the case wherein M is a single bond and the carbon atom bonded to M in A is substituted with a hydroxyl and a phenyl at the same time.

The halogen is F, Cl, Br or I, preferably F or Cl.

The straight or branched C_1–C_6 alkyl is specifically methyl, ethyl, (n-, i-)propyl, (n-, i-, s-, t-)butyl, or the like, preferably methyl or ethyl, more preferably methyl.

The straight or branched C_1–C_6 alkoxy is specifically methoxy, ethoxy, (n-, i-)propyloxy, (n-, i-, s-, t-)butyloxy, or the like, preferably methoxy or ethoxy, more preferably methoxy.

The straight or branched C_1–C_6 alkylthio is specifically methylthio, ethylthio, (n-, i-)propylthio, (n-, i-, s-, t-)butylthio, or the like, preferably methylthio or ethylthio, more preferably methylthio.

The straight or branched C_1–C_6 alkylsulfonyl is specifically methylsulfonyl, ethylsulfonyl, (n-, i-)propylsulfonyl, (n-, i-, s-, t-)butylsulfonyl, or the like, preferably methylsulfonyl or ethylsulfonyl, more preferably methylsulfonyl.

The straight or branched C_1–C_6 acyl is specifically acetyl, ethylcarbonyl, (n-, i-)propylcarbonyl, (n-, i-, s-, t-)carbonyl, or the like, preferably acetyl or ethylcarbonyl, more preferably acetyl.

The straight or branched C_1–C_6 acylamino is specifically acetylamino, ethylcarbonylamino, (n-, i-)propylcarbonylamino, (n-, i-, s-, t-)carbonylamino, or the like, preferably acetylamino or ethylcarbonylamino, more preferably acetylamino.

The trihalomethyl group is specifically trifluoromethyl, tribromomethyl or trichloromethyl, preferably trifluoromethyl.

Above all, suitable examples of A are substituted or unsubstituted straight, cyclic or branched C_1-C_7 alkylene, {which may be interrupted by one or more of atoms or groups selected from –O–, –S–, $–SO_2–$ and $–NR^3–$, (wherein NR^3 is as defined above), provided that either of these atoms or groups is not directly bonded to M}. Preferably, A is $–CH_2CH_2–$, $–CH_2CH_2CH_2–$, $–CH_2C(=O)CH_2–$, $–CH_2OCH_2–$, $–CH_2SCH_2–$, $–CH_2S(=O)CH_2–$,

$-CH_2CF_2CH_2-$, $-CH_2SO_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, $-CH_2SO_2CH_2CH_2-$, $-CH_2C(=O)CH_2CH_2-$, $-CH_2C(=O)(CH_3)_2CH_2-$, $-CH_2C(=O)C(=O)CH_2-$ or the like, more preferably $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2C(=O)CH_2-$, $-CH_2OCH_2-$, $-CH_2SCH_2-$, $-CH_2S(=O)CH_2-$, $-CH_2CF_2CH_2-$, $-CH_2SO_2CH_2-$ or $-CH_2C(CH_3)_2CH_2-$, further preferably $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2C(CH_3)_2CH_2-$, especially preferably $-CH_2CH_2CH_2-$.

E represents $-COOR^3$, $-SO_3R^3$, $-CONHR^3$, $-SO_2NHR^3$, tetrazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl or 5-oxo-1,2,4-thiadiazol-3-yl, (wherein R^3 represents hydrogen or straight or branched C_1–C_6 alkyl).

R^3 is specifically hydrogen, methyl, ethyl, (n-, i-)propyl, (n-, i-, s-, t-)butyl or the like, preferably hydrogen, methyl or ethyl, especially preferably hydrogen.

Above all, E is preferably $-COOR^3$, $-SO_3R^3$ or tetrazol-5-yl, more preferably $-COOR^3$, especially preferably –COOH.

G represents substituted or unsubstituted straight or branched C_1–C_6 alkylene, which may be interrupted by one or more of atoms or groups selected from –O–, –S–, $-SO_2-$ and $-NR^3-$, wherein R^3 is as defined above. Also, either of these heteroatoms or groups is, if present, not directly bonded to the benzimidazole ring. The substituents on the alkylene are selected from halogen, hydroxyl, nitro, cyano, straight or branched C_1–C_6 alkyl, straight or branched C_1–C_6 alkoxy (including cases wherein neighboring two form an acetal), trihalomethyl, trihalomethoxy, phenyl and oxo. Specifically G is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CO-$, $-CH_2CH_2O-$, $-CH_2CONH-$, –CO–, $-SO_2-$, $-CH_2SO_2-$, $-CH_2S-$, $-CH_2CH_2S-$ or the like, preferably $-CH_2-$, $-CH_2CH_2-$, $-CH_2CO-$ or $-CH_2CH_2O-$, more preferably $-CH_2-$ or $-CH_2CH_2-$, especially preferably $-CH_2-$. Each of the groups listed here is bonded to the 1-position (N atom) of the benzimidazole at the left side whereas it is attached to J at the right side.

M represents a single bond or $-S(O)_m-$ wherein m is an integer ranging from 0 to 2. M is preferably –S– or $-SO_2-$, especially preferably –S– .

J represents substituted or unsubstituted C_4–C_{10} heteroaryl (one or more heteroatoms selected from oxygen, nitrogen and sulfur in the ring), except for imidazole or unsubstituted pyridine ring. Furthermore, J is limited to chemically synthesizable groups.

The unsubstituted C_4–C_{10} heteroaryl (one or more heteroatoms selected from oxygen, nitrogen and sulfur in the ring) is, specifically, furyl, thienyl, thiazolyl, pyrimidinyl, oxazolyl, isoxazolyl, benzofuryl, benzimidazolyl, quinolyl, isoquinolyl, quinoxalinyl, benzoxadiazolyl, benzothiadiazolyl, indolyl, benzothiazolyl, benzothienyl, benzoisoxazolyl or the like, preferably bicyclic heteroaryl, more preferably benzofuryl, benzimidazolyl, quinolyl, isoquinolyl, quinoxalinyl, benzoxadiazolyl, benzothiadiazolyl, indolyl, benzothiazolyl, benzothienyl or benzoisoxazolyl, especially preferably benzothienyl or indolyl, further preferably benzothienyl.

The substituents on the heteroaryl described above are halogen, hydroxyl, nitro, cyano, straight or branched C_1–C_6 alkyl, straight or branched C_1–C_6 alkoxy (including cases wherein neighboring two form an acetal), straight or branched C_1–C_6 alkylthio, straight or branched C_1–C_6 alkylsulfonyl, straight or branched C_1–C_6 acyl, straight or branched C_1–C_6 acylamino, substituted or unsubstituted anilido, trihalomethyl, trihalomethoxy, phenyl or phenoxy optionally substituted with one or more halogen atoms. One or more of these substituents each may independently be present at any positions in the ring.

The halogen is F, Cl, Br or I, preferably F or Cl.

The straight or branched C_1–C_6 alkyl is specifically methyl, ethyl, (n-, i-)propyl, (n-, i-, s-, t-)butyl, or the like, preferably methyl or ethyl, further preferably methyl.

The straight or branched C_1–C_6 alkoxy is specifically methoxy, ethoxy, (n-, i-)propyloxy, (n-, i-, s-, t-)butyloxy, methylenedioxy or the like, preferably methoxy or ethoxy, further preferably methoxy.

The straight or branched C_1–C_6 alkylthio is specifically methylthio, ethylthio, (n-, i-)propylthio, (n-, i-, s-, t-)butylthio, or the like, preferably methylthio or ethylthio, further preferably methylthio.

The straight or branched C_1–C_6 alkylsulfonyl is specifically methylsulfonyl, ethylsulfonyl, (n-, i-)propylsulfonyl, (n-, i-, s-, t-)butylsulfonyl, or the like, preferably methylsulfonyl or ethylsulfonyl, further preferably methylsulfonyl.

The straight or branched C_1–C_6 acyl is specifically acetyl, ethylcarbonyl, (n-, i-)propylcarbonyl, (n-, i-, s-, t-)carbonyl, or the like, preferably acetyl or ethylcarbonyl, further

preferably acetyl.

The straight or branched C_1–C_6 acylamino is specifically acetylamino, ethylcarbonylamino, (n-, i-)propylcarbonylamino, (n-, i-, s-, t-)carbonylamino, or the like, preferably acetylamino or ethylcarbonylamino, further preferably acetylamino.

The trihalomethyl is specifically trifluoromethyl, tribromomethyl or trichloromethyl.

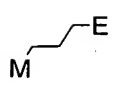
The substituent in J is preferably halogen, cyano, straight or branched C_1–C_4 alkyl, straight or branched C_1–C_4 alkoxy (including cases wherein neighboring two form an acetal) or trihalomethyl, more preferably F, Cl, cyano, methyl, methoxy or trifluoromethyl, further preferably methyl.

X represents –CH= or nitrogen, preferably –CH=.

Preferable compounds represented by formula (I) are a set of various compounds composed by each of the groups referred to as preferred. Although not to be limited, compounds listed in the following table are preferred. Above all, those particularly preferred are the compounds of No. 34, 38, 39, 41, 42, 52, 54, 56, 58, 59, 63, 135, 137, 148, 152, 154, 244, 340, 436, 514, 519, 521, 532, 534, 536, 538, 615, 628, 1112 and 1114.

In the following table A1 to A3 and J1 to J32 are groups represented by the following formulae, wherein E, G, M, m and X are as defined above. As representative examples, here are shown those wherein E is COOH, G is CH_2, M is S (m is 0) or a single bond (represented by "–" in the table) and X is –CH=, although not to be limited thereto.

A1



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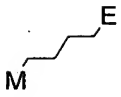

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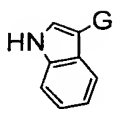
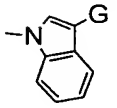


J1



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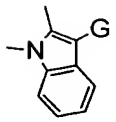

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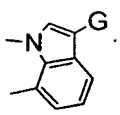

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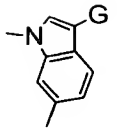

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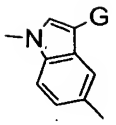
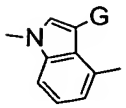
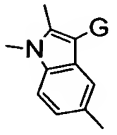


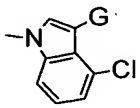
J6



J7



J8



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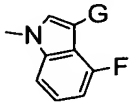

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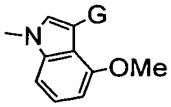

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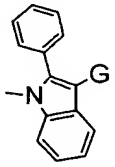

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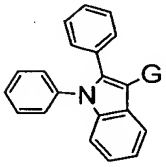
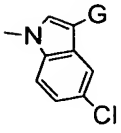
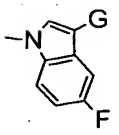


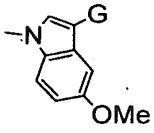
J13



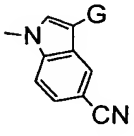
J14



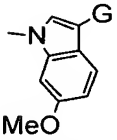
J15



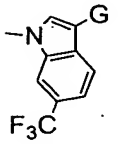
J16



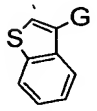
J17



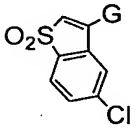
J18



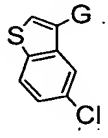
J19



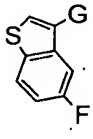
J20



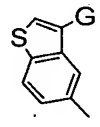
J21



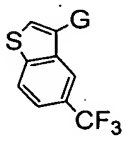
J22



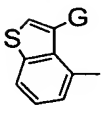
J23



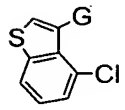
J24



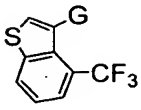
J25



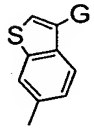
J26



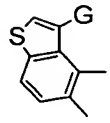
J27



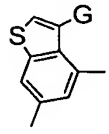
J28



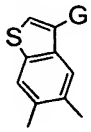
J29



J30



J31



J32

COMPOUND NO.	R1	R2	A	J	M
1	H	H	A1	J1	S
2	H	H	A1	J2	S
3	H	H	A1	J3	S
4	H	H	A1	J4	S
5	H	H	A1	J5	S
6	H	H	A1	J6	S
7	H	H	A1	J7	S
8	H	H	A1	J8	S
9	H	H	A1	J9	S
10	H	H	A1	J10	S
11	H	H	A1	J11	S
12	H	H	A1	J12	S
13	H	H	A1	J13	S
14	H	H	A1	J14	S
15	H	H	A1	J15	S
16	H	H	A1	J16	S
17	H	H	A1	J17	S
18	H	H	A1	J18	S
19	H	H	A1	J19	S
20	H	H	A1	J20	S
21	H	H	A1	J21	S
22	H	H	A1	J22	S
23	H	H	A1	J23	S
24	H	H	A1	J24	S

COMPOUND NO.	R1	R2	A	J	M
25	H	H	A1	J25	S
26	H	H	A1	J26	S
27	H	H	A1	J27	S
28	H	H	A1	J28	S
29	H	H	A1	J29	S
30	H	H	A1	J30	S
31	H	H	A1	J31	S
32	H	H	A1	J32	S
33	H	H	A2	J1	S
34	H	H	A2	J2	S
35	H	H	A2	J3	S
36	H	H	A2	J4	S
37	H	H	A2	J5	S
38	H	H	A2	J6	S
39	H	H	A2	J7	S
40	H	H	A2	J8	S
41	H	H	A2	J9	S
42	H	H	A2	J10	S
43	H	H	A2	J11	S
44	H	H	A2	J12	S
45	H	H	A2	J13	S
46	H	H	A2	J14	S
47	H	H	A2	J15	S
48	H	H	A2	J16	S

COMPOUND NO.	R1	R2	A	J	M
49	H	H	A2	J17	S
50	H	H	A2	J18	S
51	H	H	A2	J19	S
52	H	H	A2	J20	S
53	H	H	A2	J21	S
54	H	H	A2	J22	S
55	H	H	A2	J23	S
56	H	H	A2	J24	S
57	H	H	A2	J25	S
58	H	H	A2	J26	S
59	H	H	A2	J27	S
60	H	H	A2	J28	S
61	H	H	A2	J29	S
62	H	H	A2	J30	S
63	H	H	A2	J31	S
64	H	H	A2	J32	S
65	H	H	A3	J1	S
66	H	H	A3	J2	S
67	H	H	A3	J3	S
68	H	H	A3	J4	S
69	H	H	A3	J5	S
70	H	H	A3	J6	S
71	H	H	A3	J7	S
72	H	H	A3	J8	S

COMPOUND NO.	R1	R2	A	J	M
73	H	H	A3	J9	S
74	H	H	A3	J10	S
75	H	H	A3	J11	S
76	H	H	A3	J12	S
77	H	H	A3	J13	S
78	H	H	A3	J14	S
79	H	H	A3	J15	S
80	H	H	A3	J16	S
81	H	H	A3	J17	S
82	H	H	A3	J18	S
83	H	H	A3	J19	S
84	H	H	A3	J20	S
85	H	H	A3	J21	S
86	H	H	A3	J22	S
87	H	H	A3	J23	S
88	H	H	A3	J24	S
89	H	H	A3	J25	S
90	H	H	A3	J26	S
91	H	H	A3	J27	S
92	H	H	A3	J28	S
93	H	H	A3	J29	S
94	H	H	A3	J30	S
95	H	H	A3	J31	S
96	H	H	A3	J32	S

COMPOUND NO.	R1	R2	A	J	M
97	MeO	H	A1	J1	S
98	MeO	H	A1	J2	S
99	MeO	H	A1	J3	S
100	MeO	H	A1	J4	S
101	MeO	H	A1	J5	S
102	MeO	H	A1	J6	S
103	MeO	H	A1	J7	S
104	MeO	H	A1	J8	S
105	MeO	H	A1	J9	S
106	MeO	H	A1	J10	S
107	MeO	H	A1	J11	S
108	MeO	H	A1	J12	S
109	MeO	H	A1	J13	S
110	MeO	H	A1	J14	S
111	MeO	H	A1	J15	S
112	MeO	H	A1	J16	S
113	MeO	H	A1	J17	S
114	MeO	H	A1	J18	S
115	MeO	H	A1	J19	S
116	MeO	H	A1	J20	S
117	MeO	H	A1	J21	S
118	MeO	H	A1	J22	S
119	MeO	H	A1	J23	S
120	MeO	H	A1	J24	S

COMPOUND NO.	R1	R2	A	J	M
121	MeO	H	A1	J25	S
122	MeO	H	A1	J26	S
123	MeO	H	A1	J27	S
124	MeO	H	A1	J28	S
125	MeO	H	A1	J29	S
126	MeO	H	A1	J30	S
127	MeO	H	A1	J31	S
128	MeO	H	A1	J32	S
129	MeO	H	A2	J1	S
130	MeO	H	A2	J2	S
131	MeO	H	A2	J3	S
132	MeO	H	A2	J4	S
133	MeO	H	A2	J5	S
134	MeO	H	A2	J6	S
135	MeO	H	A2	J7	S
136	MeO	H	A2	J8	S
137	MeO	H	A2	J9	S
138	MeO	H	A2	J10	S
139	MeO	H	A2	J11	S
140	MeO	H	A2	J12	S
141	MeO	H	A2	J13	S
142	MeO	H	A2	J14	S
143	MeO	H	A2	J15	S
144	MeO	H	A2	J16	S

COMPOUND NO.	R1	R2	A	J	M
145	MeO	H	A2	J17	S
146	MeO	H	A2	J18	S
147	MeO	H	A2	J19	S
148	MeO	H	A2	J20	S
149	MeO	H	A2	J21	S
150	MeO	H	A2	J22	S
151	MeO	H	A2	J23	S
152	MeO	H	A2	J24	S
153	MeO	H	A2	J25	S
154	MeO	H	A2	J26	S
155	MeO	H	A2	J27	S
156	MeO	H	A2	J28	S
157	MeO	H	A2	J29	S
158	MeO	H	A2	J30	S
159	MeO	H	A2	J31	S
160	MeO	H	A2	J32	S
161	MeO	H	A3	J1	S
162	MeO	H	A3	J2	S
163	MeO	H	A3	J3	S
164	MeO	H	A3	J4	S
165	MeO	H	A3	J5	S
166	MeO	H	A3	J6	S
167	MeO	H	A3	J7	S
168	MeO	H	A3	J8	S

COMPOUND NO.	R1	R2	A	J	M
169	MeO	H	A3	J9	S
170	MeO	H	A3	J10	S
171	MeO	H	A3	J11	S
172	MeO	H	A3	J12	S
173	MeO	H	A3	J13	S
174	MeO	H	A3	J14	S
175	MeO	H	A3	J15	S
176	MeO	H	A3	J16	S
177	MeO	H	A3	J17	S
178	MeO	H	A3	J18	S
179	MeO	H	A3	J19	S
180	MeO	H	A3	J20	S
181	MeO	H	A3	J21	S
182	MeO	H	A3	J22	S
183	MeO	H	A3	J23	S
184	MeO	H	A3	J24	S
185	MeO	H	A3	J25	S
186	MeO	H	A3	J26	S
187	MeO	H	A3	J27	S
188	MeO	H	A3	J28	S
189	MeO	H	A3	J29	S
190	MeO	H	A3	J30	S
191	MeO	H	A3	J31	S
192	MeO	H	A3	J32	S

COMPOUND NO.	R1	R2	A	J	M
193	CN	H	A1	J1	S
194	CN	H	A1	J2	S
195	CN	H	A1	J3	S
196	CN	H	A1	J4	S
197	CN	H	A1	J5	S
198	CN	H	A1	J6	S
199	CN	H	A1	J7	S
200	CN	H	A1	J8	S
201	CN	H	A1	J9	S
202	CN	H	A1	J10	S
203	CN	H	A1	J11	S
204	CN	H	A1	J12	S
205	CN	H	A1	J13	S
206	CN	H	A1	J14	S
207	CN	H	A1	J15	S
208	CN	H	A1	J16	S
209	CN	H	A1	J17	S
210	CN	H	A1	J18	S
211	CN	H	A1	J19	S
212	CN	H	A1	J20	S
213	CN	H	A1	J21	S
214	CN	H	A1	J22	S
215	CN	H	A1	J23	S
216	CN	H	A1	J24	S

COMPOUND NO.	R1	R2	A	J	M
217	CN	H	A1	J25	S
218	CN	H	A1	J26	S
219	CN	H	A1	J27	S
220	CN	H	A1	J28	S
221	CN	H	A1	J29	S
222	CN	H	A1	J30	S
223	CN	H	A1	J31	S
224	CN	H	A1	J32	S
225	CN	H	A2	J1	S
226	CN	H	A2	J2	S
227	CN	H	A2	J3	S
228	CN	H	A2	J4	S
229	CN	H	A2	J5	S
230	CN	H	A2	J6	S
231	CN	H	A2	J7	S
232	CN	H	A2	J8	S
233	CN	H	A2	J9	S
234	CN	H	A2	J10	S
235	CN	H	A2	J11	S
236	CN	H	A2	J12	S
237	CN	H	A2	J13	S
238	CN	H	A2	J14	S
239	CN	H	A2	J15	S
240	CN	H	A2	J16	S

COMPOUND NO.	R1	R2	A	J	M
241	CN	H	A2	J17	S
242	CN	H	A2	J18	S
243	CN	H	A2	J19	S
244	CN	H	A2	J20	S
245	CN	H	A2	J21	S
246	CN	H	A2	J22	S
247	CN	H	A2	J23	S
248	CN	H	A2	J24	S
249	CN	H	A2	J25	S
250	CN	H	A2	J26	S
251	CN	H	A2	J27	S
252	CN	H	A2	J28	S
253	CN	H	A2	J29	S
254	CN	H	A2	J30	S
255	CN	H	A2	J31	S
256	CN	H	A2	J32	S
257	CN	H	A3	J1	S
258	CN	H	A3	J2	S
259	CN	H	A3	J3	S
260	CN	H	A3	J4	S
261	CN	H	A3	J5	S
262	CN	H	A3	J6	S
263	CN	H	A3	J7	S
264	CN	H	A3	J8	S

COMPOUND NO.	R1	R2	A	J	M
265	CN	H	A3	J9	S
266	CN	H	A3	J10	S
267	CN	H	A3	J11	S
268	CN	H	A3	J12	S
269	CN	H	A3	J13	S
270	CN	H	A3	J14	S
271	CN	H	A3	J15	S
272	CN	H	A3	J16	S
273	CN	H	A3	J17	S
274	CN	H	A3	J18	S
275	CN	H	A3	J19	S
276	CN	H	A3	J20	S
277	CN	H	A3	J21	S
278	CN	H	A3	J22	S
279	CN	H	A3	J23	S
280	CN	H	A3	J24	S
281	CN	H	A3	J25	S
282	CN	H	A3	J26	S
283	CN	H	A3	J27	S
284	CN	H	A3	J28	S
285	CN	H	A3	J29	S
286	CN	H	A3	J30	S
287	CN	H	A3	J31	S
288	CN	H	A3	J32	S

COMPOUND NO.	R1	R2	A	J	M
289	Me	H	A1	J1	S
290	Me	H	A1	J2	S
291	Me	H	A1	J3	S
292	Me	H	A1	J4	S
293	Me	H	A1	J5	S
294	Me	H	A1	J6	S
295	Me	H	A1	J7	S
296	Me	H	A1	J8	S
297	Me	H	A1	J9	S
298	Me	H	A1	J10	S
299	Me	H	A1	J11	S
300	Me	H	A1	J12	S
301	Me	H	A1	J13	S
302	Me	H	A1	J14	S
303	Me	H	A1	J15	S
304	Me	H	A1	J16	S
305	Me	H	A1	J17	S
306	Me	H	A1	J18	S
307	Me	H	A1	J19	S
308	Me	H	A1	J20	S
309	Me	H	A1	J21	S
310	Me	H	A1	J22	S
311	Me	H	A1	J23	S
312	Me	H	A1	J24	S

COMPOUND NO.	R1	R2	A	J	M
313	Me	H	A1	J25	S
314	Me	H	A1	J26	S
315	Me	H	A1	J27	S
316	Me	H	A1	J28	S
317	Me	H	A1	J29	S
318	Me	H	A1	J30	S
319	Me	H	A1	J31	S
320	Me	H	A1	J32	S
321	Me	H	A2	J1	S
322	Me	H	A2	J2	S
323	Me	H	A2	J3	S
324	Me	H	A2	J4	S
325	Me	H	A2	J5	S
326	Me	H	A2	J6	S
327	Me	H	A2	J7	S
328	Me	H	A2	J8	S
329	Me	H	A2	J9	S
330	Me	H	A2	J10	S
331	Me	H	A2	J11	S
332	Me	H	A2	J12	S
333	Me	H	A2	J13	S
334	Me	H	A2	J14	S
335	Me	H	A2	J15	S
336	Me	H	A2	J16	S

COMPOUND NO.	R1	R2	A	J	M
337	Me	H	A2	J17	S
338	Me	H	A2	J18	S
339	Me	H	A2	J19	S
340	Me	H	A2	J20	S
341	Me	H	A2	J21	S
342	Me	H	A2	J22	S
343	Me	H	A2	J23	S
344	Me	H	A2	J24	S
345	Me	H	A2	J25	S
346	Me	H	A2	J26	S
347	Me	H	A2	J27	S
348	Me	H	A2	J28	S
349	Me	H	A2	J29	S
350	Me	H	A2	J30	S
351	Me	H	A2	J31	S
352	Me	H	A2	J32	S
353	Me	H	A3	J1	S
354	Me	H	A3	J2	S
355	Me	H	A3	J3	S
356	Me	H	A3	J4	S
357	Me	H	A3	J5	S
358	Me	H	A3	J6	S
359	Me	H	A3	J7	S
360	Me	H	A3	J8	S

COMPOUND NO.	R1	R2	A	J	M
361	Me	H	A3	J9	S
362	Me	H	A3	J10	S
363	Me	H	A3	J11	S
364	Me	H	A3	J12	S
365	Me	H	A3	J13	S
366	Me	H	A3	J14	S
367	Me	H	A3	J15	S
368	Me	H	A3	J16	S
369	Me	H	A3	J17	S
370	Me	H	A3	J18	S
371	Me	H	A3	J19	S
372	Me	H	A3	J20	S
373	Me	H	A3	J21	S
374	Me	H	A3	J22	S
375	Me	H	A3	J23	S
376	Me	H	A3	J24	S
377	Me	H	A3	J25	S
378	Me	H	A3	J26	S
379	Me	H	A3	J27	S
380	Me	H	A3	J28	S
381	Me	H	A3	J29	S
382	Me	H	A3	J30	S
383	Me	H	A3	J31	S
384	Me	H	A3	J32	S

COMPOUND NO.	R1	R2	A	J	M
385	H	Me	A1	J1	S
386	H	Me	A1	J2	S
387	H	Me	A1	J3	S
388	H	Me	A1	J4	S
389	H	Me	A1	J5	S
390	H	Me	A1	J6	S
391	H	Me	A1	J7	S
392	H	Me	A1	J8	S
393	H	Me	A1	J9	S
394	H	Me	A1	J10	S
395	H	Me	A1	J11	S
396	H	Me	A1	J12	S
397	H	Me	A1	J13	S
398	H	Me	A1	J14	S
399	H	Me	A1	J15	S
400	H	Me	A1	J16	S
401	H	Me	A1	J17	S
402	H	Me	A1	J18	S
403	H	Me	A1	J19	S
404	H	Me	A1	J20	S
405	H	Me	A1	J21	S
406	H	Me	A1	J22	S
407	H	Me	A1	J23	S
408	H	Me	A1	J24	S

COMPOUND NO.	R1	R2	A	J	M
409	H	Me	A1	J25	S
410	H	Me	A1	J26	S
411	H	Me	A1	J27	S
412	H	Me	A1	J28	S
413	H	Me	A1	J29	S
414	H	Me	A1	J30	S
415	H	Me	A1	J31	S
416	H	Me	A1	J32	S
417	H	Me	A2	J1	S
418	H	Me	A2	J2	S
419	H	Me	A2	J3	S
420	H	Me	A2	J4	S
421	H	Me	A2	J5	S
422	H	Me	A2	J6	S
423	H	Me	A2	J7	S
424	H	Me	A2	J8	S
425	H	Me	A2	J9	S
426	H	Me	A2	J10	S
427	H	Me	A2	J11	S
428	H	Me	A2	J12	S
429	H	Me	A2	J13	S
430	H	Me	A2	J14	S
431	H	Me	A2	J15	S
432	H	Me	A2	J16	S

COMPOUND NO.	R1	R2	A	J	M
433	H	Me	A2	J17	S
434	H	Me	A2	J18	S
435	H	Me	A2	J19	S
436	H	Me	A2	J20	S
437	H	Me	A2	J21	S
438	H	Me	A2	J22	S
439	H	Me	A2	J23	S
440	H	Me	A2	J24	S
441	H	Me	A2	J25	S
442	H	Me	A2	J26	S
443	H	Me	A2	J27	S
444	H	Me	A2	J28	S
445	H	Me	A2	J29	S
446	H	Me	A2	J30	S
447	H	Me	A2	J31	S
448	H	Me	A2	J32	S
449	H	Me	A3	J1	S
450	H	Me	A3	J2	S
451	H	Me	A3	J3	S
452	H	Me	A3	J4	S
453	H	Me	A3	J5	S
454	H	Me	A3	J6	S
455	H	Me	A3	J7	S
456	H	Me	A3	J8	S

COMPOUND NO.	R1	R2	A	J	M
457	H	Me	A3	J9	S
458	H	Me	A3	J10	S
459	H	Me	A3	J11	S
460	H	Me	A3	J12	S
461	H	Me	A3	J13	S
462	H	Me	A3	J14	S
463	H	Me	A3	J15	S
464	H	Me	A3	J16	S
465	H	Me	A3	J17	S
466	H	Me	A3	J18	S
467	H	Me	A3	J19	S
468	H	Me	A3	J20	S
469	H	Me	A3	J21	S
470	H	Me	A3	J22	S
471	H	Me	A3	J23	S
472	H	Me	A3	J24	S
473	H	Me	A3	J25	S
474	H	Me	A3	J26	S
475	H	Me	A3	J27	S
476	H	Me	A3	J28	S
477	H	Me	A3	J29	S
478	H	Me	A3	J30	S
479	H	Me	A3	J31	S
480	H	Me	A3	J32	S

COMPOUND NO.	R1	R2	A	J	M
481	Me	Me	A1	J1	S
482	Me	Me	A1	J2	S
483	Me	Me	A1	J3	S
484	Me	Me	A1	J4	S
485	Me	Me	A1	J5	S
486	Me	Me	A1	J6	S
487	Me	Me	A1	J7	S
488	Me	Me	A1	J8	S
489	Me	Me	A1	J9	S
490	Me	Me	A1	J10	S
491	Me	Me	A1	J11	S
492	Me	Me	A1	J12	S
493	Me	Me	A1	J13	S
494	Me	Me	A1	J14	S
495	Me	Me	A1	J15	S
496	Me	Me	A1	J16	S
497	Me	Me	A1	J17	S
498	Me	Me	A1	J18	S
499	Me	Me	A1	J19	S
500	Me	Me	A1	J20	S
501	Me	Me	A1	J21	S
502	Me	Me	A1	J22	S
503	Me	Me	A1	J23	S
504	Me	Me	A1	J24	S

COMPOUND NO.	R1	R2	A	J	M
505	Me	Me	A1	J25	S
506	Me	Me	A1	J26	S
507	Me	Me	A1	J27	S
508	Me	Me	A1	J28	S
509	Me	Me	A1	J29	S
510	Me	Me	A1	J30	S
511	Me	Me	A1	J31	S
512	Me	Me	A1	J32	S
513	Me	Me	A2	J1	S
514	Me	Me	A2	J2	S
515	Me	Me	A2	J3	S
516	Me	Me	A2	J4	S
517	Me	Me	A2	J5	S
518	Me	Me	A2	J6	S
519	Me	Me	A2	J7	S
520	Me	Me	A2	J8	S
521	Me	Me	A2	J9	S
522	Me	Me	A2	J10	S
523	Me	Me	A2	J11	S
524	Me	Me	A2	J12	S
525	Me	Me	A2	J13	S
526	Me	Me	A2	J14	S
527	Me	Me	A2	J15	S
528	Me	Me	A2	J16	S

COMPOUND NO.	R1	R2	A	J	M
529	Me	Me	A2	J17	S
530	Me	Me	A2	J18	S
531	Me	Me	A2	J19	S
532	Me	Me	A2	J20	S
533	Me	Me	A2	J21	S
534	Me	Me	A2	J22	S
535	Me	Me	A2	J23	S
536	Me	Me	A2	J24	S
537	Me	Me	A2	J25	S
538	Me	Me	A2	J26	S
539	Me	Me	A2	J27	S
540	Me	Me	A2	J28	S
541	Me	Me	A2	J29	S
542	Me	Me	A2	J30	S
543	Me	Me	A2	J31	S
544	Me	Me	A2	J32	S
545	Me	Me	A3	J1	S
546	Me	Me	A3	J2	S
547	Me	Me	A3	J3	S
548	Me	Me	A3	J4	S
549	Me	Me	A3	J5	S
550	Me	Me	A3	J6	S
551	Me	Me	A3	J7	S
552	Me	Me	A3	J8	S

COMPOUND NO.	R1	R2	A	J	M
553	Me	Me	A3	J9	S
554	Me	Me	A3	J10	S
555	Me	Me	A3	J11	S
556	Me	Me	A3	J12	S
557	Me	Me	A3	J13	S
558	Me	Me	A3	J14	S
559	Me	Me	A3	J15	S
560	Me	Me	A3	J16	S
561	Me	Me	A3	J17	S
562	Me	Me	A3	J18	S
563	Me	Me	A3	J19	S
564	Me	Me	A3	J20	S
565	Me	Me	A3	J21	S
566	Me	Me	A3	J22	S
567	Me	Me	A3	J23	S
568	Me	Me	A3	J24	S
569	Me	Me	A3	J25	S
570	Me	Me	A3	J26	S
571	Me	Me	A3	J27	S
572	Me	Me	A3	J28	S
573	Me	Me	A3	J29	S
574	Me	Me	A3	J30	S
575	Me	Me	A3	J31	S
576	Me	Me	A3	J32	S

COMPOUND NO.	R1	R2	A	J	M
577	Cl	Cl	A1	J1	S
578	Cl	Cl	A1	J2	S
579	Cl	Cl	A1	J3	S
580	Cl	Cl	A1	J4	S
581	Cl	Cl	A1	J5	S
582	Cl	Cl	A1	J6	S
583	Cl	Cl	A1	J7	S
584	Cl	Cl	A1	J8	S
585	Cl	Cl	A1	J9	S
586	Cl	Cl	A1	J10	S
587	Cl	Cl	A1	J11	S
588	Cl	Cl	A1	J12	S
589	Cl	Cl	A1	J13	S
590	Cl	Cl	A1	J14	S
591	Cl	Cl	A1	J15	S
592	Cl	Cl	A1	J16	S
593	Cl	Cl	A1	J17	S
594	Cl	Cl	A1	J18	S
595	Cl	Cl	A1	J19	S
596	Cl	Cl	A1	J20	S
597	Cl	Cl	A1	J21	S
598	Cl	Cl	A1	J22	S
599	Cl	Cl	A1	J23	S
600	Cl	Cl	A1	J24	S

COMPOUND NO.	R1	R2	A	J	M
601	Cl	Cl	A1	J25	S
602	Cl	Cl	A1	J26	S
603	Cl	Cl	A1	J27	S
604	Cl	Cl	A1	J28	S
605	Cl	Cl	A1	J29	S
606	Cl	Cl	A1	J30	S
607	Cl	Cl	A1	J31	S
608	Cl	Cl	A1	J32	S
609	Cl	Cl	A2	J1	S
610	Cl	Cl	A2	J2	S
611	Cl	Cl	A2	J3	S
612	Cl	Cl	A2	J4	S
613	Cl	Cl	A2	J5	S
614	Cl	Cl	A2	J6	S
615	Cl	Cl	A2	J7	S
616	Cl	Cl	A2	J8	S
617	Cl	Cl	A2	J9	S
618	Cl	Cl	A2	J10	S
619	Cl	Cl	A2	J11	S
620	Cl	Cl	A2	J12	S
621	Cl	Cl	A2	J13	S
622	Cl	Cl	A2	J14	S
623	Cl	Cl	A2	J15	S
624	Cl	Cl	A2	J16	S

COMPOUND NO.	R1	R2	A	J	M
625	Cl	Cl	A2	J17	S
626	Cl	Cl	A2	J18	S
627	Cl	Cl	A2	J19	S
628	Cl	Cl	A2	J20	S
629	Cl	Cl	A2	J21	S
630	Cl	Cl	A2	J22	S
631	Cl	Cl	A2	J23	S
632	Cl	Cl	A2	J24	S
633	Cl	Cl	A2	J25	S
634	Cl	Cl	A2	J26	S
635	Cl	Cl	A2	J27	S
636	Cl	Cl	A2	J28	S
637	Cl	Cl	A2	J29	S
638	Cl	Cl	A2	J30	S
639	Cl	Cl	A2	J31	S
640	Cl	Cl	A2	J32	S
641	Cl	Cl	A3	J1	S
642	Cl	Cl	A3	J2	S
643	Cl	Cl	A3	J3	S
644	Cl	Cl	A3	J4	S
645	Cl	Cl	A3	J5	S
646	Cl	Cl	A3	J6	S
647	Cl	Cl	A3	J7	S
648	Cl	Cl	A3	J8	S

COMPOUND NO.	R1	R2	A	J	M
649	Cl	Cl	A3	J9	S
650	Cl	Cl	A3	J10	S
651	Cl	Cl	A3	J11	S
652	Cl	Cl	A3	J12	S
653	Cl	Cl	A3	J13	S
654	Cl	Cl	A3	J14	S
655	Cl	Cl	A3	J15	S
656	Cl	Cl	A3	J16	S
657	Cl	Cl	A3	J17	S
658	Cl	Cl	A3	J18	S
659	Cl	Cl	A3	J19	S
660	Cl	Cl	A3	J20	S
661	Cl	Cl	A3	J21	S
662	Cl	Cl	A3	J22	S
663	Cl	Cl	A3	J23	S
664	Cl	Cl	A3	J24	S
665	Cl	Cl	A3	J25	S
666	Cl	Cl	A3	J26	S
667	Cl	Cl	A3	J27	S
668	Cl	Cl	A3	J28	S
669	Cl	Cl	A3	J29	S
670	Cl	Cl	A3	J30	S
671	Cl	Cl	A3	J31	S
672	Cl	Cl	A3	J32	S

COMPOUND NO.	R1	R2	A	J	M
673	H	H	A1	J1	-
674	H	H	A1	J2	-
675	H	H	A1	J3	-
676	H	H	A1	J4	-
677	H	H	A1	J5	-
678	H	H	A1	J6	-
679	H	H	A1	J7	-
680	H	H	A1	J8	-
681	H	H	A1	J9	-
682	H	H	A1	J10	-
683	H	H	A1	J11	-
684	H	H	A1	J12	-
685	H	H	A1	J13	-
686	H	H	A1	J14	-
687	H	H	A1	J15	-
688	H	H	A1	J16	-
689	H	H	A1	J17	-
690	H	H	A1	J18	-
691	H	H	A1	J19	-
692	H	H	A1	J20	-
693	H	H	A1	J21	-
694	H	H	A1	J22	-
695	H	H	A1	J23	-
696	H	H	A1	J24	-

COMPOUND NO.	R1	R2	A	J	M
697	H	H	A1	J25	-
698	H	H	A1	J26	-
699	H	H	A1	J27	-
700	H	H	A1	J28	-
701	H	H	A1	J29	-
702	H	H	A1	J30	-
703	H	H	A1	J31	-
704	H	H	A1	J32	-
705	H	H	A2	J1	-
706	H	H	A2	J2	-
707	H	H	A2	J3	-
708	H	H	A2	J4	-
709	H	H	A2	J5	-
710	H	H	A2	J6	-
711	H	H	A2	J7	-
712	H	H	A2	J8	-
713	H	H	A2	J9	-
714	H	H	A2	J10	-
715	H	H	A2	J11	-
716	H	H	A2	J12	-
717	H	H	A2	J13	-
718	H	H	A2	J14	-
719	H	H	A2	J15	-
720	H	H	A2	J16	-

COMPOUND NO.	R1	R2	A	J	M
721	H	H	A2	J17	-
722	H	H	A2	J18	-
723	H	H	A2	J19	-
724	H	H	A2	J20	-
725	H	H	A2	J21	-
726	H	H	A2	J22	-
727	H	H	A2	J23	-
728	H	H	A2	J24	-
729	H	H	A2	J25	-
730	H	H	A2	J26	-
731	H	H	A2	J27	-
732	H	H	A2	J28	-
733	H	H	A2	J29	-
734	H	H	A2	J30	-
735	H	H	A2	J31	-
736	H	H	A2	J32	-
737	H	H	A3	J1	-
738	H	H	A3	J2	-
739	H	H	A3	J3	-
740	H	H	A3	J4	-
741	H	H	A3	J5	-
742	H	H	A3	J6	-
743	H	H	A3	J7	-
744	H	H	A3	J8	-

COMPOUND NO.	R1	R2	A	J	M
745	H	H	A3	J9	-
746	H	H	A3	J10	-
747	H	H	A3	J11	-
748	H	H	A3	J12	-
749	H	H	A3	J13	-
750	H	H	A3	J14	-
751	H	H	A3	J15	-
752	H	H	A3	J16	-
753	H	H	A3	J17	-
754	H	H	A3	J18	-
755	H	H	A3	J19	-
756	H	H	A3	J20	-
757	H	H	A3	J21	-
758	H	H	A3	J22	-
759	H	H	A3	J23	-
760	H	H	A3	J24	-
761	H	H	A3	J25	-
762	H	H	A3	J26	-
763	H	H	A3	J27	-
764	H	H	A3	J28	-
765	H	H	A3	J29	-
766	H	H	A3	J30	-
767	H	H	A3	J31	-
768	H	H	A3	J32	-

COMPOUND NO.	R1	R2	A	J	M
769	MeO	H	A1	J1	-
770	MeO	H	A1	J2	-
771	MeO	H	A1	J3	-
772	MeO	H	A1	J4	-
773	MeO	H	A1	J5	-
774	MeO	H	A1	J6	-
775	MeO	H	A1	J7	-
776	MeO	H	A1	J8	-
777	MeO	H	A1	J9	-
778	MeO	H	A1	J10	-
779	MeO	H	A1	J11	-
780	MeO	H	A1	J12	-
781	MeO	H	A1	J13	-
782	MeO	H	A1	J14	-
783	MeO	H	A1	J15	-
784	MeO	H	A1	J16	-
785	MeO	H	A1	J17	-
786	MeO	H	A1	J18	-
787	MeO	H	A1	J19	-
788	MeO	H	A1	J20	-
789	MeO	H	A1	J21	-
790	MeO	H	A1	J22	-
791	MeO	H	A1	J23	-
792	MeO	H	A1	J24	-

COMPOUND NO.	R1	R2	A	J	M
793	MeO	H	A1	J25	-
794	MeO	H	A1	J26	-
795	MeO	H	A1	J27	-
796	MeO	H	A1	J28	-
797	MeO	H	A1	J29	-
798	MeO	H	A1	J30	-
799	MeO	H	A1	J31	-
800	MeO	H	A1	J32	-
801	MeO	H	A2	J1	-
802	MeO	H	A2	J2	-
803	MeO	H	A2	J3	-
804	MeO	H	A2	J4	-
805	MeO	H	A2	J5	-
806	MeO	H	A2	J6	-
807	MeO	H	A2	J7	-
808	MeO	H	A2	J8	-
809	MeO	H	A2	J9	-
810	MeO	H	A2	J10	-
811	MeO	H	A2	J11	-
812	MeO	H	A2	J12	-
813	MeO	H	A2	J13	-
814	MeO	H	A2	J14	-
815	MeO	H	A2	J15	-
816	MeO	H	A2	J16	-

化合物 NO.	R1	R2	A	J	M
817	MeO	H	A2	J17	-
818	MeO	H	A2	J18	-
819	MeO	H	A2	J19	-
820	MeO	H	A2	J20	-
821	MeO	H	A2	J21	-
822	MeO	H	A2	J22	-
823	MeO	H	A2	J23	-
824	MeO	H	A2	J24	-
825	MeO	H	A2	J25	-
826	MeO	H	A2	J26	-
827	MeO	H	A2	J27	-
828	MeO	H	A2	J28	-
829	MeO	H	A2	J29	-
830	MeO	H	A2	J30	-
831	MeO	H	A2	J31	-
832	MeO	H	A2	J32	-
833	MeO	H	A3	J1	-
834	MeO	H	A3	J2	-
835	MeO	H	A3	J3	-
836	MeO	H	A3	J4	-
837	MeO	H	A3	J5	-
838	MeO	H	A3	J6	-
839	MeO	H	A3	J7	-
840	MeO	H	A3	J8	-

COMPOUND NO.	R1	R2	A	J	M
841	MeO	H	A3	J9	-
842	MeO	H	A3	J10	-
843	MeO	H	A3	J11	-
844	MeO	H	A3	J12	-
845	MeO	H	A3	J13	-
846	MeO	H	A3	J14	-
847	MeO	H	A3	J15	-
848	MeO	H	A3	J16	-
849	MeO	H	A3	J17	-
850	MeO	H	A3	J18	-
851	MeO	H	A3	J19	-
852	MeO	H	A3	J20	-
853	MeO	H	A3	J21	-
854	MeO	H	A3	J22	-
855	MeO	H	A3	J23	-
856	MeO	H	A3	J24	-
857	MeO	H	A3	J25	-
858	MeO	H	A3	J26	-
859	MeO	H	A3	J27	-
860	MeO	H	A3	J28	-
861	MeO	H	A3	J29	-
862	MeO	H	A3	J30	-
863	MeO	H	A3	J31	-
864	MeO	H	A3	J32	-

COMPOUND NO.	R1	R2	A	J	M
865	CN	H	A1	J1	-
866	CN	H	A1	J2	-
867	CN	H	A1	J3	-
868	CN	H	A1	J4	-
869	CN	H	A1	J5	-
870	CN	H	A1	J6	-
871	CN	H	A1	J7	-
872	CN	H	A1	J8	-
873	CN	H	A1	J9	-
874	CN	H	A1	J10	-
875	CN	H	A1	J11	-
876	CN	H	A1	J12	-
877	CN	H	A1	J13	-
878	CN	H	A1	J14	-
879	CN	H	A1	J15	-
880	CN	H	A1	J16	-
881	CN	H	A1	J17	-
882	CN	H	A1	J18	-
883	CN	H	A1	J19	-
884	CN	H	A1	J20	-
885	CN	H	A1	J21	-
886	CN	H	A1	J22	-
887	CN	H	A1	J23	-
888	CN	H	A1	J24	-

COMPOUND NO.	R1	R2	A	J	M
889	CN	H	A1	J25	-
890	CN	H	A1	J26	-
891	CN	H	A1	J27	-
892	CN	H	A1	J28	-
893	CN	H	A1	J29	-
894	CN	H	A1	J30	-
895	CN	H	A1	J31	-
896	CN	H	A1	J32	-
897	CN	H	A2	J1	-
898	CN	H	A2	J2	-
899	CN	H	A2	J3	-
900	CN	H	A2	J4	-
901	CN	H	A2	J5	-
902	CN	H	A2	J6	-
903	CN	H	A2	J7	-
904	CN	H	A2	J8	-
905	CN	H	A2	J9	-
906	CN	H	A2	J10	-
907	CN	H	A2	J11	-
908	CN	H	A2	J12	-
909	CN	H	A2	J13	-
910	CN	H	A2	J14	-
911	CN	H	A2	J15	-
912	CN	H	A2	J16	-

COMPOUND NO.	R1	R2	A	J	M
913	CN	H	A2	J17	-
914	CN	H	A2	J18	-
915	CN	H	A2	J19	-
916	CN	H	A2	J20	-
917	CN	H	A2	J21	-
918	CN	H	A2	J22	-
919	CN	H	A2	J23	-
920	CN	H	A2	J24	-
921	CN	H	A2	J25	-
922	CN	H	A2	J26	-
923	CN	H	A2	J27	-
924	CN	H	A2	J28	-
925	CN	H	A2	J29	-
926	CN	H	A2	J30	-
927	CN	H	A2	J31	-
928	CN	H	A2	J32	-
929	CN	H	A3	J1	-
930	CN	H	A3	J2	-
931	CN	H	A3	J3	-
932	CN	H	A3	J4	-
933	CN	H	A3	J5	-
934	CN	H	A3	J6	-
935	CN	H	A3	J7	-
936	CN	H	A3	J8	-

COMPOUND NO.	R1	R2	A	J	M
937	CN	H	A3	J9	-
938	CN	H	A3	J10	-
939	CN	H	A3	J11	-
940	CN	H	A3	J12	-
941	CN	H	A3	J13	-
942	CN	H	A3	J14	-
943	CN	H	A3	J15	-
944	CN	H	A3	J16	-
945	CN	H	A3	J17	-
946	CN	H	A3	J18	-
947	CN	H	A3	J19	-
948	CN	H	A3	J20	-
949	CN	H	A3	J21	-
950	CN	H	A3	J22	-
951	CN	H	A3	J23	-
952	CN	H	A3	J24	-
953	CN	H	A3	J25	-
954	CN	H	A3	J26	-
955	CN	H	A3	J27	-
956	CN	H	A3	J28	-
957	CN	H	A3	J29	-
958	CN	H	A3	J30	-
959	CN	H	A3	J31	-
960	CN	H	A3	J32	-

COMPOUND NO.	R1	R2	A	J	M
961	Me	Me	A1	J1	-
962	Me	Me	A1	J2	-
963	Me	Me	A1	J3	-
964	Me	Me	A1	J4	-
965	Me	Me	A1	J5	-
966	Me	Me	A1	J6	-
967	Me	Me	A1	J7	-
968	Me	Me	A1	J8	-
969	Me	Me	A1	J9	-
970	Me	Me	A1	J10	-
971	Me	Me	A1	J11	-
972	Me	Me	A1	J12	-
973	Me	Me	A1	J13	-
974	Me	Me	A1	J14	-
975	Me	Me	A1	J15	-
976	Me	Me	A1	J16	-
977	Me	Me	A1	J17	-
978	Me	Me	A1	J18	-
979	Me	Me	A1	J19	-
980	Me	Me	A1	J20	-
981	Me	Me	A1	J21	-
982	Me	Me	A1	J22	-
983	Me	Me	A1	J23	-
984	Me	Me	A1	J24	-

COMPOUND NO.	R1	R2	A	J	M
985	Me	Me	A1	J25	-
986	Me	Me	A1	J26	-
987	Me	Me	A1	J27	-
988	Me	Me	A1	J28	-
989	Me	Me	A1	J29	-
990	Me	Me	A1	J30	-
991	Me	Me	A1	J31	-
992	Me	Me	A1	J32	-
993	Me	Me	A2	J1	-
994	Me	Me	A2	J2	-
995	Me	Me	A2	J3	-
996	Me	Me	A2	J4	-
997	Me	Me	A2	J5	-
998	Me	Me	A2	J6	-
999	Me	Me	A2	J7	-
1000	Me	Me	A2	J8	-
1001	Me	Me	A2	J9	-
1002	Me	Me	A2	J10	-
1003	Me	Me	A2	J11	-
1004	Me	Me	A2	J12	-
1005	Me	Me	A2	J13	-
1006	Me	Me	A2	J14	-
1007	Me	Me	A2	J15	-
1008	Me	Me	A2	J16	-

COMPOUND NO.	R1	R2	A	J	M
1009	Me	Me	A2	J17	-
1010	Me	Me	A2	J18	-
1011	Me	Me	A2	J19	-
1012	Me	Me	A2	J20	-
1013	Me	Me	A2	J21	-
1014	Me	Me	A2	J22	-
1015	Me	Me	A2	J23	-
1016	Me	Me	A2	J24	-
1017	Me	Me	A2	J25	-
1018	Me	Me	A2	J26	-
1019	Me	Me	A2	J27	-
1020	Me	Me	A2	J28	-
1021	Me	Me	A2	J29	-
1022	Me	Me	A2	J30	-
1023	Me	Me	A2	J31	-
1024	Me	Me	A2	J32	-
1025	Me	Me	A3	J1	-
1026	Me	Me	A3	J2	-
1027	Me	Me	A3	J3	-
1028	Me	Me	A3	J4	-
1029	Me	Me	A3	J5	-
1030	Me	Me	A3	J6	-
1031	Me	Me	A3	J7	-
1032	Me	Me	A3	J8	-

COMPOUND NO.	R1	R2	A	J	M
1033	Me	Me	A3	J9	-
1034	Me	Me	A3	J10	-
1035	Me	Me	A3	J11	-
1036	Me	Me	A3	J12	-
1037	Me	Me	A3	J13	-
1038	Me	Me	A3	J14	-
1039	Me	Me	A3	J15	-
1040	Me	Me	A3	J16	-
1041	Me	Me	A3	J17	-
1042	Me	Me	A3	J18	-
1043	Me	Me	A3	J19	-
1044	Me	Me	A3	J20	-
1045	Me	Me	A3	J21	-
1046	Me	Me	A3	J22	-
1047	Me	Me	A3	J23	-
1048	Me	Me	A3	J24	-
1049	Me	Me	A3	J25	-
1050	Me	Me	A3	J26	-
1051	Me	Me	A3	J27	-
1052	Me	Me	A3	J28	-
1053	Me	Me	A3	J29	-
1054	Me	Me	A3	J30	-
1055	Me	Me	A3	J31	-
1056	Me	Me	A3	J32	-

COMPOUND NO.	R1	R2	A	J	M
1057	H	MeO	A1	J1	S
1058	H	MeO	A1	J2	S
1059	H	MeO	A1	J3	S
1060	H	MeO	A1	J4	S
1061	H	MeO	A1	J5	S
1062	H	MeO	A1	J6	S
1063	H	MeO	A1	J7	S
1064	H	MeO	A1	J8	S
1065	H	MeO	A1	J9	S
1066	H	MeO	A1	J10	S
1067	H	MeO	A1	J11	S
1068	H	MeO	A1	J12	S
1069	H	MeO	A1	J13	S
1070	H	MeO	A1	J14	S
1071	H	MeO	A1	J15	S
1072	H	MeO	A1	J16	S
1073	H	MeO	A1	J17	S
1074	H	MeO	A1	J18	S
1075	H	MeO	A1	J19	S
1076	H	MeO	A1	J20	S
1077	H	MeO	A1	J21	S
1078	H	MeO	A1	J22	S
1079	H	MeO	A1	J23	S
1080	H	MeO	A1	J24	S

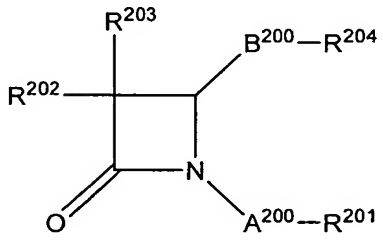
COMPOUND NO.	R1	R2	A	J	M
1081	H	MeO	A1	J25	S
1082	H	MeO	A1	J26	S
1083	H	MeO	A1	J27	S
1084	H	MeO	A1	J28	S
1085	H	MeO	A1	J29	S
1086	H	MeO	A1	J30	S
1087	H	MeO	A1	J31	S
1088	H	MeO	A1	J32	S
1089	H	MeO	A2	J1	S
1090	H	MeO	A2	J2	S
1091	H	MeO	A2	J3	S
1092	H	MeO	A2	J4	S
1093	H	MeO	A2	J5	S
1094	H	MeO	A2	J6	S
1095	H	MeO	A2	J7	S
1096	H	MeO	A2	J8	S
1097	H	MeO	A2	J9	S
1098	H	MeO	A2	J10	S
1099	H	MeO	A2	J11	S
1100	H	MeO	A2	J12	S
1101	H	MeO	A2	J13	S
1102	H	MeO	A2	J14	S
1103	H	MeO	A2	J15	S
1104	H	MeO	A2	J16	S

COMPOUND NO.	R1	R2	A	J	M
1105	H	MeO	A2	J17	S
1106	H	MeO	A2	J18	S
1107	H	MeO	A2	J19	S
1108	H	MeO	A2	J20	S
1109	H	MeO	A2	J21	S
1110	H	MeO	A2	J22	S
1111	H	MeO	A2	J23	S
1112	H	MeO	A2	J24	S
1113	H	MeO	A2	J25	S
1114	H	MeO	A2	J26	S
1115	H	MeO	A2	J27	S
1116	H	MeO	A2	J28	S
1117	H	MeO	A2	J29	S
1118	H	MeO	A2	J30	S
1119	H	MeO	A2	J31	S
1120	H	MeO	A2	J32	S
1121	H	MeO	A3	J1	S
1122	H	MeO	A3	J2	S
1123	H	MeO	A3	J3	S
1124	H	MeO	A3	J4	S
1125	H	MeO	A3	J5	S
1126	H	MeO	A3	J6	S
1127	H	MeO	A3	J7	S
1128	H	MeO	A3	J8	S

COMPOUND NO.	R1	R2	A	J	M
1129	H	MeO	A3	J9	S
1130	H	MeO	A3	J10	S
1131	H	MeO	A3	J11	S
1132	H	MeO	A3	J12	S
1133	H	MeO	A3	J13	S
1134	H	MeO	A3	J14	S
1135	H	MeO	A3	J15	S
1136	H	MeO	A3	J16	S
1137	H	MeO	A3	J17	S
1138	H	MeO	A3	J18	S
1139	H	MeO	A3	J19	S
1140	H	MeO	A3	J20	S
1141	H	MeO	A3	J21	S
1142	H	MeO	A3	J22	S
1143	H	MeO	A3	J23	S
1144	H	MeO	A3	J24	S
1145	H	MeO	A3	J25	S
1146	H	MeO	A3	J26	S
1147	H	MeO	A3	J27	S
1148	H	MeO	A3	J28	S
1149	H	MeO	A3	J29	S
1150	H	MeO	A3	J30	S
1151	H	MeO	A3	J31	S
1152	H	MeO	A3	J32	S

The benzimidazole derivatives represented by formula (I) may be converted to medically acceptable non-toxic salts, if necessary. The salts include salts with alkaline metal ions such as Na^+ and K^+; salts with alkaline earth metal ions such as Mg^{2+} and Ca^{2+}; salts with metal ions such as Al^{3+} and Zn^{2+}; ammonia; salts with organic bases such as triethylamine, ethylenediamine, propanediamine, pyrrolidine, piperidine, piperazine, pyridine, lysine, choline, ethanolamine, N,N-dimethylethanolamine, 4-hydroxypiperidine, glucosamine, N-methylglucamine and the like. Above all, salts with Na^+, K^+, Ca^{2+}, lysine, choline, N,N-dimethylethanolamine or N-methylglucamine are preferred. Furthermore, salts with acids can be prepared. Such an acid includes for example, mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and carbonic acid; and organic acids such as maleic acid, citric acid, malic acid, tartaric acid, fumaric acid, methanesulfonic acid, trifluoroacetic acid, formic acid and the like. Further, compounds of formula (II) include racemic form, both enantiomers and all the stereoisomers (diastereomers, epimers, enantiomers and the like).

Chymase inhibitors in the present invention also include compounds represented by the following formula (II) described in WO 00/05204:

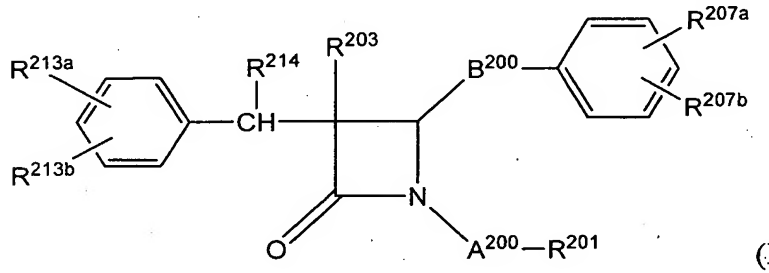


(II)

[wherein A^{200} represents a single bond, –CO–, –COO–, –COCO–, –CONH– or $–SO_2–$, R^{201} represents lower alkyl optionally having substituents, lower alkenyl optionally having substituents, lower alkynyl optionally having substituents, cycloalkyl optionally having substituents, cycloalkenyl optionally having substituents or aryl optionally having substituents, and R^{201} may be hydrogen when A^{200} is a single bond, –CO–, –COCO–, –CONH– or $–SO_2–$, R^{202} and R^{203} represent independently hydrogen, halogen, lower alkyl optionally having substituents, lower alkoxycarbonyl optionally having substituents, acyl optionally having substituents, amino optionally having substituents, carbamoyl optionally having substituents or

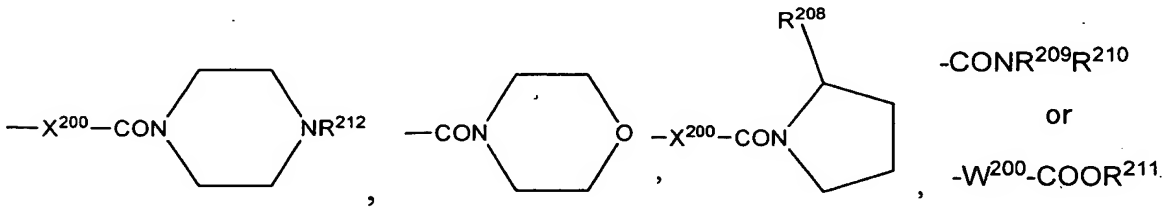
aryl optionally having substituents, B^{200} represents a single bond, –S–, –O–, –S–S–, –SO– or $–SO_2–$, and R^{204} represents hydrogen, lower alkyl optionally having substituents, aryl optionally having substituents or heterocyclyl optionally having substituents , wherein R^{204} may be acyl optionally having substituents when B^{200} is a single bond, –S–, –O–, –SO– or $–SO_2–$].

Another example of the chymase inhibitor is the compound or a prodrug, pharmaceutically acceptable salt or hydrate thereof represented by formula (II'):



(II')

(wherein A^{200} and R^{201} are as defined for formula (II), R^{203} represents hydrogen, halogen, lower alkoxycarbonyl optionally having substituents, acyl optionally having substituents, amino optionally having substituents, aryl optionally having substituents or benzyl optionally having substituents, R^{213a} and R^{213b} each independently represent hydrogen, halogen, hydroxyl, lower alkyl optionally having substituents, lower alkoxy optionally having substituents, amino optionally having substituents or lower alkylthio optionally having substituents, or R^{213a} and R^{213b} taken together form lower alkylenedioxy, R^{214} represents hydrogen, hydroxyl, lower alkyl, lower alkoxy or acyloxy, R^{207a} represents hydrogen,



(wherein X^{200} and W^{200} represent a single bond, methylene or vinylene, R^{208} represents methyl or carbamoyl, R^{209} represents hydrogen or lower alkyl, R^{210} represents lower alkyl optionally having substituents (lower alkylamino; phenyl optionally substituted with halogen; carboxyl; or lower alkoxycarbonyl optionally substituted with aryl), lower alkenyl, lower alkylamino,

phenylamino, phenyl or benzenesulfonyl, R^{211} represents hydrogen or lower alkyl optionally having substituents (lower alkylamino; acyloxy; phenyl optionally substituted with halogen or methylenedioxy; or heterocyclyl), and

R^{212} represents C_1–C_3 alkyl or cyclohexyl);

R^{207b} is hydrogen, and B^{200} is O or S).

Still another example of the chymase inhibitor is 4-[1-[N-[bis(4-methylphenyl)methyl]-carbamoyl]-3-(2-ethoxybenzyl)-4-oxoazetidin-2-yloxy]benzoic acid, 4-[1-{[bis(4-methoxyphenyl)methyl]carbamoyl}-3-(2-ethoxybenzyl)-4-oxoazetidin-2-yloxy] benzoic acid or (6R,7R)-3-[1-(carboxymethyl)tetrazol-5-ylsulfanylmethyl]-7-methoxy-7-(2-methoxybenzamido)-1-oxa-3-cephem-4-carboxylic acid 3-methylbenzyl ester or prodrug, pharmaceutically acceptable salt or hydrate thereof.

In formula (II) each of the terms is defined as follows:

A "halogen" includes F, Cl, Br or I, preferably Cl or Br.

A "lower alkyl" means straight or branched alkyl having 1 to 10, preferably 1 to 6, more preferably 1 to 3 carbon atoms, specifically methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, isohexyl, heptyl, isoheptyl, octyl, isooctyl, nonyl, decyl or the like.

"A lower alkyl optionally having substituents" includes for example, lower alkyl optionally substituted at any position with one or more substituents selected from hydroxyl, halogen, lower alkoxy, carboxy, acyl, acyloxy, cycloalkyl, lower alkoxycarbonyl optionally having substituents (amino optionally substituted with lower alkyl, aryl or the like), amino optionally having substituents (lower alkyl, acyl or the like), carbamoyl, aryl optionally having substituents [halogen, lower alkyl optionally having substituents {carboxy, lower alkoxycarbonyl optionally having substituents (aryl, alkylamino or the like), lower alkenyloxycarbonyl optionally having substituents (aryl, alkylamino or the like), aryloxycarbonyl optionally having substituents (aryl, alkylamino or the like), or heterocyclylcarbonyl optionally having substituents (lower alkyl, carbamoyl or the like)}, lower alkenyl optionally having substituents {carboxy, lower alkoxycarbonyl optionally having substituents (aryl, alkylamino or the like), lower alkenyloxycarbonyl, aryloxycarbonyl,

or heterocyclylcarbonyl optionally having substituents (lower alkyl, carbamoyl or the like) or the like}, lower alkoxy, carboxy, lower alkoxycarbonyl, aryl, acyl, amino optionally having substituents (lower alkyl or the like), carbamoyl optionally having substituents {lower alkyl optionally having substituents (lower alkylamino, aryl or the like); lower alkenyl optionally having substituents (lower alkylamino, aryl or the like), or aryl optionally having substituents (lower alkylamino, aryl or the like)}, aryloxy, heterocyclyl, heterocyclylcarbonyl optionally having substituents (lower alkyl, carbamoyl or the like), or lower alkylenedioxy], heterocyclyl, and heterocyclylcarbonyl optionally having substituents (lower alkyl or the like). Preferred examples of lower alkyl substituted with optionally substituted aryl are unsubstituted benzyl, lower alkyoxybenzyl and diphenylmethyl.

The alkyl moiety of "lower alkoxy", "lower alkoxycarbonyl", "lower alkylamino" or "lower alkylthio" is as defined by "lower alkyl", and the substituent thereon, if present, is the same as that on the alkyl described above.

A "lower alkenylene" includes straight or branched C_1–C_6 alkylene, for example, methylene, ethylene, trimethylene, tetramethylene, propylene, ethylethylene and the like, preferably methylene.

A "lower alkylenedioxy" includes methylenedioxy, ethylenedioxy and the like, preferably methylenedioxy.

A "lower alkenyl" includes straight or branched alkenyl having 2 to 10, preferably 2 to 6, more preferably 2 to 4 carbon atoms. Specifically it includes vinyl, 1-propenyl, allyl, isopropenyl, butenyl, isobutenyl, butadienyl, pentenyl, isopentenyl, pentadienyl, hexenyl, isohexenyl, hexadienyl, heptenyl, octenyl, nonenyl, decenyl and the like, and it has one or more double bonds at arbitrary positions. The substituent in the "lower alkenyl optionally having substituents" includes hydroxyl, halogen, lower alkoxy, carboxy, acyl, acyloxy, cycloalkyl, lower alkoxycarbonyl, aryl, heterocyclyl, heterocyclylcarbonyl optionally having substituents (lower alkyl, carbamoyl or the like) and the like. These substituents may be present at one or more arbitrary positions in the lower alkenyl.

The lower alkenyl moiety in "lower alkenyloxycarbonyl" and the substituents in "optionally substituted lower alkenyloxycarbonyl" are the same as those defined above.

A "lower alkenylene" includes, for example, groups having one or more double bonds at arbitrary positions in the "lower alkylene" described above having 2 to 6, preferably 2 to 4 carbon atoms. It includes specifically vinylene, propenylene, butenylene, pentenylene, methylpropenylene and the like.

A "lower alkynyl" refers to straight or branched alkynyl or the like having 2 to 10, preferably 2 to 6, more preferably 2 to 4 carbon atoms and specifically includes ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl and the like. These groups have one or more triple bonds at arbitrary positions and may also have double bonds. The substituent in the "lower alkynyl optionally having substituents" is the same as defined for the lower alkenyl.

An "acyl" includes aliphatic acyl having 1 to 10, preferably 1 to 6, more preferably 1 to 3 carbon atoms, aroyl and the like. Specifically it includes formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, pivaloyl, hexanoyl, acryloyl, propioloyl, methacryloyl, crotonoyl, cyclohexanecarbonyl, benzoyl and the like. The substituent in "acyl optionally having substituents" includes hydroxyl, halogen, lower alkoxy, carboxy, lower alkoxycarbonyl, aryl, heterocyclyl and the like. These substituents may be present at one or more arbitrary positions.

The acyl moiety in "acyloxy" or "acylamino" and the substituents in "acyloxy optionally having substituents" or "acylamino optionally having substituents" are the same as defined for the acyl described above. A preferred example of the acyloxy is acetyloxy.

A "cycloalkyl" refers to for example, three- to six-membered carbocyclyl or the like. Specifically it includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. The substituent in "cycloalkyl optionally having substituents" includes hydroxyl, halogen, lower alkoxycarbonyl, lower alkoxy, aryl, heterocyclyl and the like. These substituents may be present at one or more arbitrary positions.

A "cycloalkenyl" refers to a group having one or more double bonds at any positions in the ring of the cycloalkyl described above. Specifically it includes cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl and the like. The substituent in "cycloalkenyl optionally having substituents" is the same as that defined for the cycloalkyl described above. These substituents may be present at one or more arbitrary positions. An

"amino optionally having substituents" includes substituted amino and unsubstituted amino. It may be substituted with one or more hydroxyl, halogen, lower alkyl, lower alkylamino, acyl, carbamoyl, aryl, heterocyclyl or the like.

A "carbamoyl optionally having substituents" includes substituted carbamoyl and unsubstituted carbamoyl. The substituent therein is selected from lower alkyl optionally having substituents (for example, unsubstituted lower alkyl), lower alkenyl optionally having substituents (for example, unsubstituted lower alkenyl), lower alkylsulfonyl, sulfamoyl, acyl optionally having substituents (such as halogen), amino, aryl optionally having substituents (for example, unsubstituted aryl) and the like.

An "aryl" includes phenyl, naphthyl, anthracenyl, indenyl, phenanthrenyl and the like. Particularly phenyl is preferred.

The substituent in "aryl optionally having substituents" includes: hydroxyl, halogen, lower alkyl optionally having substituents [halogen, carboxy, lower alkoxycarbonyl optionally having substituents (lower alkylamino, aryl or the like), lower alkenyloxy carbonyl optionally having substituents (lower alkylaminoaryl or the like), aryloxycarbonyl optionally having substituents (lower alkylamino, aryl or the like), or heterocyclylcarbonyl optionally having substituents (lower alkyl, carbamoyl or the like)], lower alkenyl optionally having substituents [halogen, carboxy, lower alkoxycarbonyl optionally having substituents (lower alkylamino, aryl or the like), lower alkenyloxycarbonyl optionally having substituents (lower alkylamino, aryl or the like), aryloxycarbonyl optionally having substituents (lower alkylamino, aryl or the like), or heterocyclylcarbonyl optionally having substituents (lower alkyl, carbamoyl or the like)], lower alkoxy optionally having substituents (hydroxyl, halogen, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, lower alkylamino or the like), carboxy, lower alkoxycarbonyl optionally having substituents (acyloxy; lower alkylamino; aryl optionally substituted with alkylenedioxy or halogen; heterocyclyl or the like), lower alkenyloxycarbonyl, lower alkylenedioxy, acyl, acyloxy, amino optionally having substituents (lower alkyl, acyl or the like), nitro, carbamoyl optionally having substituents [lower alkyl optionally having substituents (carboxy; amino optionally substituted with lower alkyl or aroyl; lower alkoxycarbonyl optionally substituted with aryl; halogen; aryl optionally substituted with

lower alkyl or lower alkoxy; or the like), cycloalkyl optionally having substituents (aryl or the like), lower alkenyl optionally having substituents (lower alkylamino, aryl or the like), amino optionally having substituents (lower alkyl, aryl or the like), aryl optionally having substituents (lower alkylamino, aryl or the like), arylsulfonyl or the like], aryl, aryloxy, heterocyclyl and heterocyclylcarbonyl optionally having substituents (lower alkyl, arylalkyl optionally substituted with lower alkylenedioxy; cycloalkyl, carbamoyl, heterocyclyl or the like). These substituents may be present at one or more arbitrary positions. The aryl moiety in "aryloxy", "arylsulfonyl" and "arylamino" is the same as "aryl" defined above, and the substituent in " aryloxy optionally having substituents " and "arylsulfonyl optionally having substituents " are the same as that on the aryl described above.

A "benzyl optionally having substituents" may have, at the methylene moiety, substituent defined as the substituent in the "lower alkyl optionally having substituents" or lower alkyl. It may have, at the phenyl moiety, substituent defined as the substituent in the "aryl optionally having substituents". The substituent on the methylene moiety includes specifically lower alkyl, aryl and the like.

A "heterocyclyl" refers to a heterocycle the ring of which contains one or more heteroatoms selected from O, S and N. It includes specifically five- or six-membered aromatic heterocyclyls such as pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, isoxazolyl, oxazolyl, oxadiazolyl, isothiazolyl, thiazolyl, thiadiazolyl, furyl, thienyl and the like, fused aromatic heterocyclyls such as indolyl, benzimidazolyl, indazolyl, indolizinyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, naphthyridinyl, quinoxalinyl, pteridinyl, benzisoxazolyl, benzoxazolyl, xadiazolyl, benzisothiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl and benzothienyl and the like, and alicyclic heterocyclyls such as ethyleneoxizinyl, dioxanyl, thiiranyl, oxathiolanyl, azetidinyl, thianyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl and morpholinyl.

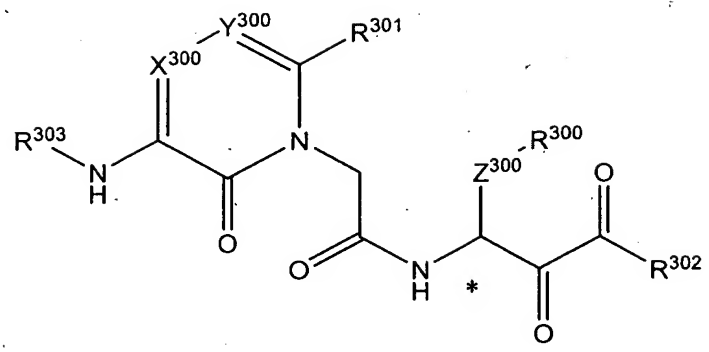
The substituent in "heterocyclyl optionally having substituents" includes hydroxyl, halogen, lower alkyl optionally having substituents (for example, unsubstituted lower alkyl), lower alkenyl, lower alkoxy, carboxy, lower alkoxycarbonyl, carbamoyl optionally having

substituents (for example, unsubstituted carbamoyl), aryl, heterocyclyl and the like. These substituents may be present at one or more arbitrary positions. The heterocyclyl moiety and substituent in "heterocyclylcarbonyl" and "heterocyclylcarbonyl optionally having substituents" are the same as in the "heterocyclyl" and the substituent in the "heterocyclyl optionally having substituents", respectively. Preferred examples of the "heterocyclylcarbonyl" are morpholylcarbonyl, piperazinylcarbonyl, methylpiperazinylcarbonyl, pyrimidinylpiperazinylcarbonyl, cyclohexylpiperazinylcarbonyl, piperidylcarbonyl, bipiperidylcarbonyl and the like.

Pharmaceutically acceptable salts of compound (II) are for example, salt with mineral acid such as hydochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrofluoric acid, hydrobromic acid and the like; salt with organic acid such as formic acid, acetic acid, tartaric acid, lactic acid, citric acid, fumaric acid, succinic acid and the like; ammonium salt; salt with organic base such as trimethylammonium, triethylammonium and the like; salt with alkaline metal such as sodium and potassium; salt with alkaline earth metal such as magnesium and calcium. The compound of formula (II) includes hydrate thereof wherein any number of water molecules may be conjugated with one molecule of (II), (II') or (II"). Furthermore, compound of formula (II) includes racemic form, both enantiomers and all stereoisomers (diastereomers, epimers, enantiomers and the like).

Among the chymase inhibitors represented by formula (II) it has already been reported that 4-[1-{[bis(4-methylphenyl)methyl]carbamoyl}-3-(2-ethoxybenzyl)-4-oxoazetizin-2-yloyl]benzoic acid has an effect on a hamster model of myocardial infarction when administrated alone (Life Sci. 2002, vol. 71, p. 437). Therefore it can be expected that this compound can be remarkably effective on various diseases associated with glucose intolerance.

Another example of the chymase inhibitor in the present invention is the compound disclosed in WO 98/09949 represented by formula (III):



(III)

[wherein:

R^{300} is phenyl, which may have one or more substituents selected from group A^{300} defined below, (wherein A^{300} is halogen, nitro, hydroxyl, lower alkoxy, lower alkyl or halogenated lower alkyl);

R^{301} is (III-i) aryl, (III-ii) heteroaryl or (III-iii) straight, branched or cyclic C_1–C_6 alkyl and each independently may have one or more substituents defined in group A^{300}; or R^{301} may have, on group (III-i) – (III-iii), one or more substituents selected from group B^{300}, wherein group B^{300} is OR^{300a}, $COOR^{300a}$, $CONR^{300b}R^{300c}$, $NR^{300b}R^{300c}$, $NR^{300b}CHO$, $NR^{300b}COR^{300a}$, SO_2OR^{300a}, SO_2R^{300a}, $CONR^{300b}SO_2R^{300a}$ or $P(O)(OR^{300a})_2$ (wherein, R^{300a}–R^{300c} are independently hydrogen, lower alkyl or substituted lower alkyl; or R^{300a}–R^{300c} are independently aryl(C_1–C_7)alkyl, heteroaryl(C_1–C_7)alkyl, aryl or heteroaryl wherein the ring of aryl or heteroaryl may have one or more, usually one to three substituents selected from group A defined above and the lower alkyl has one to three substituents selected from halogen, nitro and hydroxyl); or R^{301} may have on group (III-i) – (III-iii) one or more substituents selected from cyclic group G^{300} defined below, (wherein G represents five- or six-membered heterocyclyl having one to three oxygen or nitrogen and optionally has substituents);

R^{302} is C_1–C_8 alkyl, aryl(C_1–C_7)alkyl, heteroaryl(C_1–C_7)alkyl or aryl; or R^{302} is group B^{300} defined above, C_1–C_8 alkyl substituted with group B^{300} or C_1–C_8 alkyl substituted with cyclic group G^{300} defined above;

R^{303} is hydrogen; or R^{303} is acyl represented by (i) $D^{300}(CH_2)_{0-3}CO$, (ii) $D^{300}COE^{300}CO$ or (iii) $D^{300}SO_2E^{300}CO$; or R^{303} is sulfonyl represented by $D^{300}(CH_2)_{0-3}SO_2$ or $D^{300}COE^{300}SO_2$ (wherein group D^{300} is hydrogen, straight, branched or cyclic C_1–C_6 alkyl, aryl, halogenated lower alkyl, halogenated lower alkoxy, amino, lower alkoxyamino, halogenated lower

alkylamino, $R^{300b}R^{300c}N$, $R^{300b}R^{300c}NO$, $R^{300a}O$, R^{300a}, $R^{300a}OCO$, $R^{300b}R^{300c}NCO$, $R^{300a}SO_2NR^{300b}$, $R^{300a}S$, or cyclic group G^{300} defined above and group E^{300} represents divalent bridging group having 1 to 6 carbon atoms); or R^{303} is urea represented by $R^{300b}R^{300c}NCO$; or R^{303} is thiourea represented by $R^{300b}R^{300c}NCS$; or R^{303} is R^{300a};

X^{300} and Y^{300} are each independently nitrogen or carbon and may be substituted with a group represented by R^{300a}–R^{300c}; and

Z^{300} is polymethylene wherein each hydrogen may be independently substituted with R^{300a} or R^{300b}].

Other examples of the chymase inhibitor includes:

acetamide derivative represented by formula (III) and pharmacologically acceptable salt thereof wherein R^{300} is unsubstituted phenyl, R^{301} is unsubstituted phenyl, R^{302} is unsubstituted C_1–C_8 alkyl or C_1–C_8 alkyl having substituents selected from pyrrolidin-1-yl, pyridyloxy, 2-oxo-1,2-dihydropyridin-1-yl, pyrimidyloxy, pyrazyloxy, pyridazyloxy, lower alkyl-substituted piperazin-1-yl and lower alkyl-substituted piperazin-1-ylcarbonyl, X^{300} is unsubstituted carbon, Y^{300} is nitrogen and Z^{300} is $–CH_2–$, 2-(5-substituted 6-oxo-2-phenyl-1,6-dihydropyrimidin-1-yl)-N-{2,3-dioxo-6-(2-pyridyloxy)-1-phenylmethyl}hexylacetamide, wherein the substituent is amino, t-butyloxycarbonylamino, benzylsulfonylamino, formylamino, benzylaminosulfonylamino, 4-pyridylmethyloxycarbonylamino or acetylamino, and N-[1-benzyl-2,3-dioxo-6-(2-pyridyloxy)hexyl]-2-[5-(formylamino)-6-oxo-2-phenyl-1,6,-dihydropyrimidin-1-yl]acetamide.

In the compound of formula (III), group A^{300} is selected from halogen, hydroxyl, lower alkoxy, lower alkyl or halogenated lower alkyl;

Group B^{300} is selected from OR^{300a}, $COOR^{300a}$, $CONR^{300b}R^{300c}$, $NR^{300b}R^{300c}$, $NR^{300b}CHO$, $NR^{300b}COR^{300a}$, SO_2OR^{300a}, SO_2R^{300a}, $CONR^{300b}$, SO_2R^{300a} or $P(O)(OR^{300a})_2$;

R^{300a}–R^{300c} are independently hydrogen, lower alkyl, aryl(C_1–C_7)alkyl, heteroaryl(C_1–C_7)alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl ring may have one or more substituents selected from group A defined above;

Cyclic group G^{300} is five- or six-membered heterocyclyl having 1 to 3 oxygen or nitrogen

atoms and may have substituents;

Group D^{300} is hydrogen, straight, branched or cyclic C_1–C_6 alkyl, halogenated lower alkyl such as trifluoromethyl, halogenated lower alkoxy such as 2,2,2-trifluoroethoxy, lower alkoxyamino such as methoxyamino, halogenated lower alkylamino such as 2,2,2-trifluoroethylamino, $R^{300b}R^{300c}N$, $R^{300b}R^{300c}NO$, $R^{300a}O$, R^{300a}, $R^{300a}OCO$, $R^{300b}R^{300c}NCO$, $R^{300a}SO_2NR^{300b}$, $R^{300a}S$ or group G^{300} defined above;

Group E^{300} is divalent bridging group having 1 to 6 carbon atoms and may contain 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur. For example, group E^{300} includes phenylene, which is a divalent benzene nucleus, heteroarylene, which is a divalent heteroaryl nucleus, 1,4-piperazindiyl, straight or branched aliphatic divalent bridging group having 1 to 6 carbon atoms such as methylene, dimethylene, trimethylene and 2-methyltrimethylene, alicyclic bridging group such as cyclohexylene, 1,4-cyclohexadienylene and the like.

In formula (III) each of the terms is defined as follows:

The halogen represents F, Cl, Br or I.

The alkyl chain in the alkyl, alkoxy or the like represents straight, branched or cyclic alkyl, and the number of carbon atoms is preferably between 1 and 20;

The lower alkyl and the lower alkoxy are either straight or branched group having 1 to 6 carbon atoms. The lower acyloxy represents acyloxy with an alkyl chain having 1 to 6 carbon atoms. The aryl represents phenyl or ortho-fused carbocyclyl or hetero-carbocyclyl that has 9 to 10 atoms in the rings and at least one aromatic ring. The heteroaryl contains 2 to 4 heteroatoms selected from carbon, oxygen, nitrogen and sulfur, and it is either five- or six-membered monocyclic aromatic group or ortho-fused hetero-heterocyclic group having about 8 to 10 atoms composing the rings.

The compound of formula (III), due to the presence of a chiral carbon marked by "*" in formula (III), exists as either a single enantiomer or racemic form. When a compound of formula (III) contains another chiral atom, it exists as either a single diastereomer or a mixture of diastereomers. Either of them can be isolated. In the present invention compound of formula (III) includes each of the diastereomers and diastereomeric mixture and furthermore it includes each of the enantiomers and enantiomeric mixture.

As those engaged in this field understand, the adjacent-dicarbonyl moiety in formula (III) sometimes exists as solvate, particularly hydrate. Therefore, the compound represented by formula (III) includes solvates thereof.

Besides the solvates described above, some of the compounds represented by formula (III) exist as various polymorphic forms such as a tautomer of solvate. Therefore, the present invention comprises all the compounds that have inhibitory activity against chymotrypsin-like enzymes, including any polymorphic form, racemic and optically active forms and solvates.

The following demonstrates examples of the groups in formula (III), which are not limitation but merely examples.

Preferable groups for A^{300} are F, Cl, Br, nitro, hydroxyl, methyl, ethyl and methoxy.

R^{300a}, R^{300b} and R^{300c} are for example, hydrogen, lower alkyl such as methyl, ethyl, propyl, butyl, isopropyl and the like, aryl(C_1–C_7)alkyl such as benzyl, phenethyl, phenylpropyl and the like, heteroaryl(C_1–C_7)alkyl such as pyridylmethyl, pyridylethyl, pyridylpropyl, furylmethyl, furylethyl, furylpropyl and the like, aryl such as phenyl, halogenated phenyl and the like or heteroaryl such as pyridyl, pyrimidyl, furyl, thienyl and the like.

OR^{300a} in group B^{300}, group D^{300} or the like is, for example, hydroxyl, methoxy, ethoxy, propyloxy, isopropyloxy, butoxy, benzyloxy, pyridylmethyloxy, phenoxy, pyridyloxy, pyrrolidinoxy and the like.

$COOR^{300a}$ in group B^{300}, group D^{300} or the like is, for example, methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, isopropyloxycarbonyl, butoxycarbonyl, benzyloxycarbonyl, pyridylmethyloxycarbonyl, phenoxycarbonyl and the like.

$CONR^{300b}R^{300c}$ in group B^{300}, group D^{300} or the like is, for example, dimethylaminocarbonyl, methylethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl and the like.

$NR^{300b}R^{300c}$ in group B^{300}, group D^{300} or the like is, for example, monomethylamino, dimethylanimo, methylethylamino, diethylamino, dipropylamino and the like. $NR^{300b}CHO$ in group B^{300} or the like is, for example, formylamino, formylmethylamino and the like. $NR^{300b}COR^{300a}$ in group B^{300} or the like is, for example, methylcarbonylamino, ethylcarbonylamino, propylcarbonylamino, methylcarbonylmethylamino and the like.

SO_2OR^{300a} in group B or the like is, for example, sulfonic acid group and the like. SO_2R^{300a} in group B^{300} or the like is, for example, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, t-butylsulfonyl, benzylsulfonyl, toluenesulfonyl, benzenesulfonyl, formaminobenzenesulfonyl, nitrobenzenesulfonyl, methoxybenzenesulfonyl, pyridylsulfonyl, pyridylmethylsulfonyl, trifluoromethylsulfonyl and the like.

$CONR^{300b}SO_2R^{300a}$ in group B^{300} or the like is, for example, methylsulfonylaminocarbonyl, phenylsulfonylaminocarbonyl, phenylmethylaminosulfonylcarbonyl and the like. $P(O)(OR^{300a})_2$ in group B^{300} or the like is, for example, diethylphosphono, diphenylphosphono, dibenzylphosphono and the like. Preferable groups for B^{300} are methoxy, ethoxy, propyloxy, isopropyloxy, phenylmethyloxy, phenethyloxy, phenylpropyloxy, pyridylmethyloxy, pyridylethyloxy, pyridylpropyloxy, furylmethyloxy, furylethyloxy, furylpropyloxy, pyridyloxyethyloxy, pyridyloxypropyloxy and the like.

Group G^{300} is, for example, five- or six-membered heteroaryl or five- or six-membered alicyclic group having heteroatoms, preferably 4-morpholin-4-yl, 4-methylpiperazin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, 2-oxo-1,2-dihydropyridin-1-yl or 2-pyridyloxy. Preferable groups for D^{300} are hydrogen, methyl, cyclohexyl, phenyl, pyridyl, trifluoromethyl, 2,2,2-trifluoroethyloxy, methyloxyamino, 2,2,2-trifluoroethylamino, phenylmethylamino and the like.

$D^{300}(CH_2)_{0-3}CO$ in R^{303} is for example, formyl, acetyl, propionyl, cyclopropanecarbonyl, valeryl, butyryl, cyclopropylmethylcarbonyl, pivaloyl, trifluoroacetyl, phenylacetyl, 3-phenylpropionyl, pyridylcarbonyl, benzoyl, tetrahydro-2-furoyl, tetrahydro-3-furoyl, methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, isopropyloxycarbonyl, butyloxycarbonyl, t-butyloxycarbonyl, benzyloxycarbonyl, 9-fluorenyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, allyloxycarbonyl, hydroxyoxalyl and the like.

The acyl group represented by $D^{300}COE^{300}CO$ or $D^{300}SO_2E^{300}CO$ in R^{303} is, for example, 4-[1-(4-morpholin-1-yl)carbonyl]benzenecarbonyl, [4-(1-pyrrolidin-1-yl)carbonyl]benzenecarbonyl,

[4-(1-piperidin-1-yl)carbonyl]benzenecarbonyl, phenylsulfonylaminocarbonyl and the like.

$D^{303}(CH_2)_{0-3}SO_2$ in R^{303} is, for example, toluenesulfonyl, benzenesulfonyl, formaminobenzenesulfonyl, nitrobenzenesulfonyl, methoxybenzenesulfonyl, pyridylsulfonyl, pyridylmethylsulfonyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, t-butylsulfonyl, benzylsulfonyl, trifluoromethylsulfonyl, phenacylsulfonyl, aminosulfonyl, methylaminosulfonyl, ethylaminosulfonyl, propylaminosulfonyl, isopropylaminosulfonyl, butylaminosulfonyl, t-butylaminosulfonyl, phenylaminosulfonyl, benzylaminosulfonyl, pyridylaminosulfonyl, pyridylmethylaminosulfonyl and the like.

$D^{300}COE^{300}SO_2$ in R^{303} is, for example, benzoylaminosulfonyl and the like.

The thiourea represented by $R^{300b}R^{300c}NCS$ in R^{303}, is for example, methylaminothiocarbonyl, ethylaminothiocarbonyl, propylaminothiocarbonyl, butylaminothiocarbonyl, isopropylaminothiocarbonyl, valerylaminothiocarbonyl, benzylaminothiocarbonyl and the like.

A preferred group for R^{300} is phenyl, which may have 1 to 4 substituents selected from halogen, nitro, hydroxyl, lower alkoxy, lower alkyl and trifluoromethyl, as group A^{300} on the ring thereof.

Preferred groups for R^{301} are phenyl, furyl, thienyl and pyridyl, which may have one or two substituents selected from group A^{300} on the ring thereof.

Preferred groups for R^{302} are C_1–C_4 alkyl, aryl(C_1–C_3)alkyl and G^{300}(C_1–C_3) alkyl substituted with a group selected from group G^{300} defined above. More preferred groups are methyl, ethyl, propyl, butyl, isopropyl, benzyl, phenethyl, phenylpropyl, pyridylmethyl, pyridylethyl, pyridylpropyl, furylmethyl, furylethyl, furylpropyl, pyridyloxymethyl, pyridyloxyethyl, pyridyloxypropyl, piperazin-1-yl(C_1–C_3)alkyl optionally substituted at the 4-position with a group selected from methyl, ethyl, propyl, butyl, isopropyl, benzyl and pyridylmethyl, piperidin-1-yl(C_1–C_3)alkyl, 4-morpholin-4-yl(C_1–C_3)alkyl, 2-pyridyloxy(C_1–C_3)alkyl, pyrrolidin-1-yl(C_1–C_3)alkyl, 2-oxo-1,2-dihydropyridin-1-yl(C_1–C_3)alkyl, methoxycarbonyl(C_0–C_3)alkyl, ethoxycarbonyl(C_0–C_3)alkyl, propyloxycarbonyl(C_0–C_3)alkyl, butyloxycarbonyl(C_0–C_3)alkyl, benzyloxycarbonyl(C_0–C_3)alkyl, t-butoxycarbonyl(C_0–C_3)alkyl,

phenyloxycarbonyl(C_0–C_3)alkyl, nitrophenyloxycarbonyl(C_0–C_3)alkyl and bromophenyloxycarbonyl(C_0–C_3)alkyl. Furthermore preferred groups are methyl, ethyl, propyl, butyl, phenylpropyl, 4-morpholin-4-yl(C_1–C_3)alkyl, 2-oxo-1,2-dihydropyridin-1-yl(C_1–C_3)alkyl, 2-pyridyloxy(C_1–C_3)alkyl, ethoxycarbonyl(C_0–C_3)alkyl and 4-methylpiperazin-1-ylcarbonyl(C_1–C_3)alkyl.

R^{303} is preferably hydrogen, formyl, acetyl, propionyl, cyclopropanecarbonyl, valeryl, butyryl, cyclopropylmethylcarbonyl, pivaloyl, trifluoroacetyl, phenylacetyl, 3-phenylpropionyl, pyridylcarbonyl, benzoyl, tetrahydro-2-furoyl, tetrahydro-3-furoyl, methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, isopropyloxycarbonyl, butyloxycarbonyl, t-butyloxycarbonyl, benzyloxycarbonyl, 9-fluorenyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, allyloxycarbonyl, hydroxyoxalyl, 4-[1-(4-morpholin-4-yl)carbonyl]benzenecarbonyl, [4-(1-pyrrolidin-1-yl)carbonyl]benzenecarbonyl, [4-(1-piperidin-1-yl)carbonyl]benzenecarbonyl, toluenesulfonyl, benzenesulfonyl, formaminobenzenesulfonyl, nitrobenzenesulfonyl, methoxybenzenesulfonyl, pyridylsulfonyl, pyridylmethylsulfonyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, t-butylsulfonyl, benzylsulfonyl, trifluoromethylsulfonyl, phenacylsulfonyl, aminosulfonyl, methylaminosulfonyl, ethylaminosulfonyl, propylaminosulfonyl, isopopylaminosulfonyl, butylaminosulfonyl, t-butylaminosulfonyl, phenylaminosulfonyl, benzylaminosulfonyl, pyridylaminosulfonyl, pyridylmethylaminosulfonyl, methylaminothiocarbonyl, ethylaminothiocarbonyl, propylaminothiocarbonyl, butylaminothiocarbonyl, isopropylaminothiocarbonyl, valerylaminothiocarbonyl, benzylaminothiocarbonyl (wherein, the phenyl or heteroaryl ring, if present, may be substituted with one or two halogen or methyl), or methyl, ethyl, propyl, isopropyl, butyl, t-butyl, benzyl, phenethyl, thiazolyl, pyridylmethyl or 5-tetrazolylmethyl (wherein, the phenyl or heteroaryl ring, if present, may be substituted with one or two halogen or methyl).

X^{300} and Y^{300} are preferably carbon or nitrogen.

Z^{300} is preferably polymethylene having 1 to 3 carbon atoms, more preferably methylene.

Particularly valuable groups for the straight or branched C_1–C_8 alkyl are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, amyl, isoamyl, hexyl, heptyl and octyl. Particularly valuable groups for the cyclic alkyl are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Valuable groups for the alkylene moiety in the aryl(C_1–C_7)alkyl or heteroaryl(C_1–C_7)alkyl are methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene and heptamethylene. A particularly valuable group for the aryl is phenyl. Particularly valuable groups for the heteroaryl are pyridyl, pyrimidinyl, furyl and thienyl. Preferred groups for the aryl(C_1–C_7)alkyl are phenylmethyl, phenylethyl, phenylpropyl, phenylisopropyl, phenylbutyl, phenylisobutyl, phenylamyl, phenylisoamyl, phenylhexyl, phenylheptyl and the like. Preferred groups for the heteroaryl(C_1–C_7)alkyl are, wherein the heteroaryl is pyridyl, pyrimidinyl, furyl or thienyl, ones having the same alkyl moiety as the phenyl described above.

Particularly valuable groups for the lower alkyl are methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl. Particularly valuable groups for the lower alkoxy are methoxy, ethoxy, propyloxy, isopropyloxy and butoxy. Particularly valuable groups for the halogen are F, Cl and Br.

A particular group of compound (III) consists of compounds wherein R^{300}, R^{302}, R^{303}, X^{300}, Y^{300} and Z^{300} are selected from each of the groups described above and R^{301} is phenyl.

A more specified group of compound (III) consists of compounds wherein each of the symbols is as follows:

R^{300} is phenyl, which may have one to three substituents selected from halogen, hydroxyl, lower alkoxy, lower alkyl and trifluoromethyl as group A^{300}.

R^{301} is phenyl, which may have one or more substituents independently selected from group A^{300} defined as described above; or R^{301} may have one or more substituents selected from group B^{300}, which contains OR^{300a}, $COOR^{300a}$, $CONR^{300b}R^{300c}$, $NR^{300b}R^{300c}$, $NR^{300b}CHO$, $NR^{300b}COR^{300a}$, SO_2OR^{300a}, SO_3R^{300a}, $CONR^{300b}SO_2R^{300a}$ and $P(O)(OR^{300a})_2$.

R^{302} is pyridyloxy(C_1–C_4)alkyl.

R^{303} is hydrogen; or R^{303} is acyl represented by (i) $D^{300}(CH_2)_{0-3}CO$, (ii) $D^{300}COE^{300}CO$ or (iii) $D^{300}SO_2E^{300}CO$; or R^{303} is sulfonyl represented by $D^{300}(CH_2)_{0-3}SO_2$ or $D^{300}COE^{300}SO_2$ (wherein, group D^{300} represents hydrogen, straight, branched or cyclic C_1–C_6

alkyl, trifluoromethyl, 2,2,2-trifluoroethoxy, 2,2,2-trifluoroethylamino, $COOR^{300a}$, $CONR^{300b}R^{300c}$, $NR^{300b}R^{300c}$ or group G^{300} defined above; or R^{303} is thiourea represented by $R^{300b}R^{300c}NCS$ and group E^{300} is independently phenyl, heteroaryl, 1,4-piperazindiyl, cyclohexyl or 1,4-cyclohexadienyl); or R^{303} is R^{300a}.

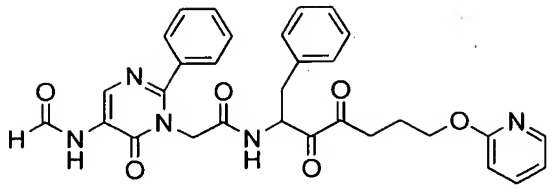
X^{300} and Y^{300} are each independently nitrogen or unsubstituted carbon.

Z^{300} is $-CH_2-$, wherein the two hydrogen atoms may be independently substituted with R^{300a} or R^{300b}.

A particular group of more specified compound (I) consists of compounds wherein R^{300} is phenyl (which may contain one or two substituents independently selected from halogen, hydroxyl and methyl), R^{302} is methyl, butyl, phenylpropyl, 4-morpholin-4-yl-propyl, 1-(ethoxycarbonyl)propyl, 4-methylpiperazin-1-ylpropyl, 2-oxo-1,2-dihydropyridin-1-yl-propyl, or 2-pyridyloxypropyl, R^{303} is hydrogen or formyl, X^{300} and Y^{300} are unsubstituted carbon or nitrogen, and Z^{300} is unsubstituted methylene. In a further specified case, R^{300} is phenyl, 3-fluorophenyl, 4-fluoropheyl, 3,4-difluorophenyl, 3,5-difluorophenyl or 3-fluoro-4-hydroxyphenyl.

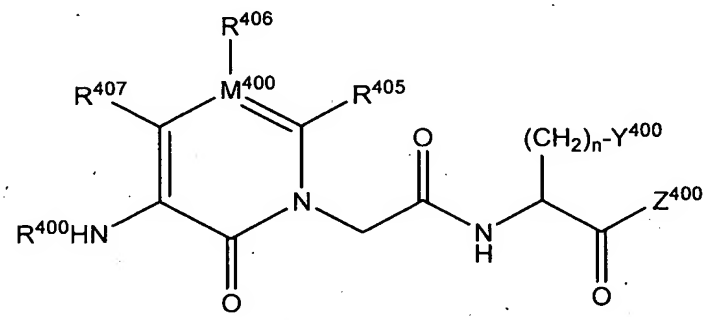
Also, pharmacologically acceptable salts of compound (III) are not particularly limited. For example, when compound (III) is acidic, the pharmacologically acceptable salt thereof includes alkali metal salts, alkaline earth metal salts, aluminum salts, ammonium salts and salts with pharmaceutically acceptable cations derived from organic bases such as primary or tertiary lower alkylamines. (B) when compound (III) is basic, pharmacologically acceptable salts thereof include acid addition salts that generate pharmaceutically acceptable anions, wherein the acid addition salts are formed by using, for example, hydrochloric acid, sulfuric acid, sulfonic acid, phosphoric acid and the like.

In particular, among the compounds represented by formula (III), it has been reported that the compound shown by the following formula (III-I) is effective in a canine model of myocardial infarction through oral administration (The 75th annual meeting report of The Japanese Pharmacological Society), hence it is expected that this compound will be useful as a chymase inhibitor in the present invention.



(III-I)

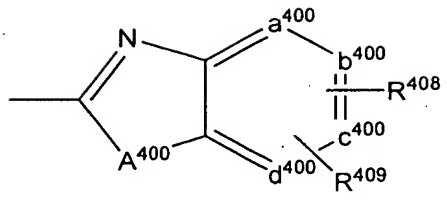
The chymase inhibitor in the present invention also includes the heterocyclic amide compounds represented by formula (IV) and pharmacologically acceptable salts thereof disclosed in WO 98/18794:



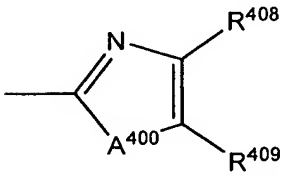
(IV)

[wherein

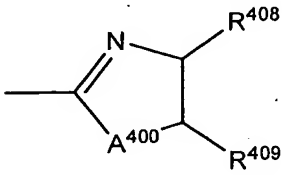
R^{400} is hydrogen, alkyl, –CHO, $–CONH_2$, $–COR^{401}$, $–COOR^{401}$, $–CONHOR^{401}$, $–CONHR^{401}$, $–CONR^{401}R^{401'}$, $–CONHSO_2R^{401}$, $–COSR^{401}$, $–COCOR^{402}$, $–COCOOR^{402}$, $–CONHCOOR^{402}$, $–COCONR^{403}R^{404}$, $–CSX^{400}R^{401}$, $–SO_2WR^{401}$, $–SO_2NR^{401}R^{401'}$ or $–SO_2E^{400}$ (wherein R^{401} and $R^{401'}$ may be the same or different and each independently represent alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl; R^{402}, R^{403} and R^{404} may be the same or different and each independently represent hydrogen, alkyl or arylalkyl, or $–NR^{403}R^{404}$ taken together may represent heterocyclyl, X^{400} represents a single bond, –NH–, –O– or –S–, W^{400} represents a single bond, –NH–, –NHCO–, –NHCOO– or –NHCONH–, and E^{400} represents hydroxyl or amino), R^{405}, R^{406} and R^{407} may be the same or different, and either each independently represent hydrogen or alkyl or one of them is selected from aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl and heteroarylalkenyl with the other being hydrogen, M^{400} represents carbon or nitrogen, wherein R^{406} is absent if M^{400} is nitrogen, Y^{400} represents cycloalkyl, aryl or heteroaryl, Z^{400} represents the groups shown by formulas (IV-i), (IV-ii) and (IV-iii):



(IV-i)



(IV-ii)



(IV-iii)

{wherein R^{408} and R^{409} may be the same or different and each independently represent hydrogen, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halogen, trifluoromethyl, cyano, nitro, $-NR^{410}R^{410'}$, $-NHSO_2R^{410}$, $-OR^{410}$, $-COOR^{410}$, $-CONHSO_2R^{410}$ or $-CONR^{410}R^{410'}$ (wherein R^{410} and $R^{410'}$ may be the same or different and each independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl or trifluoromethyl, or $-NR^{410}R^{410'}$ taken together may represent heterocyclyl), A^{400} represents –O–, –S– or $-NR^{412}$–, (wherein R^{412} represents hydrogen, alkyl, clycloalkyl or cycloalkylalkyl), and a^{400}, b^{400}, c^{400} and d^{400} are all carbon or one of them is nitrogen with the rest being carbon}, and n is 0 or 1.

In addition, each of the alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heterocyclyl and heterocyclyl alkyl described above may have substituents].

As the chymase inhibitor may also be used the heterocyclic amide compound represented by formula (IV) or pharmacologically acceptable salts thereof wherein Y^{400} is aryl optionally having substituents, Z^{400} is the group represented by formula (IV-i), and one of R^{405}, R^{406} and R^{407} is aryl optionally having substituents with the other being hydrogen (R^{406} is absent if M is nitrogen), 2-[2-[2-[5-amino-2-(3-methoxyphenyl)-6-oxo-1,6-dihydropyrimidin-1-yl]acetamido]-3-phenylpropionyl] benzoxazole-5-carboxylic acid methyl ester, and

2-[2-[5-amino-2-(4-fluorophenyl)-6-oxo-1,6-dihydropyrimidin-1-yl]acetamido]-3-phenylpropionyl)benzoxazole-5-carboxylic acid methyl ester.

Each of the terms in the formula (IV) is defined as follows:

The alkyl as R^{400}, R^{401}, $R^{401'}$, R^{402}–R^{410}, $R^{410'}$ or R^{412} is straight or branched alkyl having preferably 1 to 6 carbon atoms, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl and the like.

The cycloalkyl as R^{401}, $R^{401'}$, R^{410}, $R^{410'}$, R^{412} or Y^{400} is preferably three- to seven-membered cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

The cycloalkylalkyl as R^{401}, $R^{401'}$, R^{410}, $R^{410'}$or R^{412} comprises the cycloalkyl described above and a straight or branched alkyl having preferably 1 to 3 carbon atoms. The examples are cyclopropylmethyl, 2-cyclobutylethyl, 3-cyclopentylpropyl, cyclohexylmethyl, 2-cyclohexylethyl, cycloheptylmethyl and the like.

The aryl as R^{401}, $R^{401'}$, R^{405}–R^{410}, $R^{410'}$ or Y^{400} is preferably phenyl, naphthyl, ortho-fused bicyclic groups having 8 to 10 atoms composing the rings and at least one aromatic ring (for example, indenyl) and the like.

The arylalkyl as R^{401}, $R^{401'}$, R^{402}–R^{410} or $R^{410'}$ comprises the aryl described above and a straight or branched alkyl having preferably 1 to 3 carbon atoms. The examples are benzyl, phenethyl, 3-phenylpropyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-(1-naphthyl)ethyl, 2-(2-naphthyl)ethyl, 3-(1-naphthyl)propyl, 3-(2-naphthyl)propyl and the like. The arylalkenyl as R^{405}–R^{407} comprises the aryl described above and a straight or branched alkenyl having preferably 2 to 6 carbon atoms. The examples are styryl, 3-phenyl-2-propenyl, 4-phenyl-3-butenyl, 5-phenyl-4-pentenyl, 6-phenyl-5-hexenyl, 3-(1-naphthyl)-2-propenyl, 4-(2-naphthyl)-3-butenyl and the like.

The heteroaryl as R^{401}, $R^{401'}$, R^{405}–R^{410}, $R^{410'}$ or Y^{400} includes preferably five- or six-membered heteroaryl consisting of carbon atoms and 1 to 4 heteroatoms (oxygen, nitrogen or sulfur), ortho-fused bicyclic heteroaryl having 8 to 10 atoms composing the rings derived therefrom, particularly benzo-derivatives or derivatives fused with propenylene, trimethylene or tetramethylene and stable N-oxide thereof. The examples are pyrrolyl, furyl, thienyl,

oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazoyl, pyrazolyl, triazolyl, tetrazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, chromenyl, isoindolyl, indolyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzoxazinyl and the like.

The heteroarylalkyl as R^{401}, $R^{401'}$, R^{405}–R^{410} or $R^{410'}$ comprises the heteroaryl described above and a straight or branched alkyl having preferably 1 to 3 carbon atoms. The examples are 2-pyrrolylmethyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-thienylmethyl, 2-(2-pyridyl)ethyl, 2-(3-pyridyl)ethyl, 2-(4-pyridyl)ethyl, 3-(2-pyrrolyl)propyl and the like.

The heteroarylalkenyl as R^{405}–R^{407} comprises the heteroaryl described above and a straight or branched alkenyl having preferably 2 to 6 carbon atoms. The examples are 2-(2-pyridyl)ethenyl, 3-(2-pyridyl)-2-propenyl, 4-(3-pyridyl)-3-butenyl, 5-(2-pyrrolyl)-4-pentenyl, 6-(2-thienyl)-5-hexenyl and the like. The heterocyclyl represented by R^{401} or $R^{401'}$ is four- to six-membered cyclic group consisting of carbon atoms and 1 to 4 heteroatoms (oxygen, nitrogen or sulfur), for example, azetidinyl, pyrrolidinyl, piperidinyl, piperidino, piperazinyl, morpholinyl, morpholino, thiomorpholinyl, oxothiomorpholinyl, dioxothiomorpholinyl, tetrahydropyranyl, dioxacyclohexyl and the like.

The heterocyclyl represented by $-NR^{403}R^{404}$ or $-NR^{410}R^{410'}$ is four- to six-membered cyclic group consisting of carbon atoms and at least one nitrogen atom, which may further contain other heteroatoms (oxygen or sulfur). The examples are azetidinyl, pyrrolidinyl, piperidino, piperazinyl, morpholino, thiomorpholino, oxothiomorpholino, dioxothiomorpholino and the like.

The heterocyclylalkyl as R^{401} or $R^{401'}$ comprises the heterocyclyl defined above (R^{401} or $R^{401'}$) and a straight or branched alkyl having preferably 1 to 3 carbon atoms. The examples are azetidinylethyl, pyrrolidinylpropyl, piperidinylmethyl, piperidinoethyl, piperazinylethyl, morpholinylpropyl, morpholinomethyl, thiomorpholinylethyl, oxothiomorpholinylethyl, dioxothiomorpholinylethyl, tetrahydropyranylpropyl, dioxacyclohexylmethyl and the like.

The halogen as R^{408} or R^{409} includes F, Cl, Br and I.

In addition, among the substituents described above, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heterocyclyl and heterocyclylalkyl each may be optionally substituted with one or more substituents described below.

The substituents on the substituents include halogen, hydroxyl, nitro, cyano, trifluoromethyl, alkyl, alkoxy, alkylthio, formyl, acyloxy, oxo, phenyl, arylalkyl, $-COOR^{400a}$, $-CH_2COOR^{400a}$, $-OCH_2COOR^{400a}$, $-CONR^{400b}R^{400c}$, $-CH_2CONR^{400b}R^{400c}$, $-OCH_2CONR^{400b}R^{400c}$, $-COO(CH_2)_2NR^{400e}R^{400f}$, $-SO_2T^{401}$, $-CONR^{400d}SO_2T^{401}$, $-NR^{400e}R^{400f}$, $-NR^{400g}CHO$, $-NR^{400g}COT^{402}$, $-NR^{400g}COOT^{402}$, $-NR^{400h}CQ^{400}NR^{400i}R^{400j}$, $-NR^{400k}SO_2T^{403}$, $-SO_2NR^{401}R^{400m}$, $-SO_2NR^{400n}COT^{404}$ and the like.

In the substituents on the substituents described above, the halogen, alkyl and arylalkyl are the same as defined earlier. The alkoxy comprises a straight or branched chain of preferably 1 to 6 carbon atoms. The examples are methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy and the like. The alkylthio comprises a straight or branched chain of preferably 1 to 6 carbon atoms. The examples are methylthio, ethylthio, propylthio, butylthio, pentylthio, hexylthio and the like.

The acyloxy comprises a straight or branched chain of preferably 1 to 6 carbon atoms. The examples are formyloxy, acetyloxy, propionyloxy, butyryloxy, valeryloxy, pivaloyloxy, hexanoyloxy and the like.

In addition, R^{400a}–R^{400n} represents hydrogen, alkyl (same as described above) or arylalkyl (same as described above). Further, $-NR^{400b}R^{400c}$, $-NR^{400e}R^{400f}$, $-NR^{400i}R^{400j}$ or $-NR^{401}R^{400m}$ taken together may represent heterocyclyl (which is the same as exemplified for $-NR^{403}R^{404}$ or $-NR^{410}R^{410'}$ and may be substituted with the substituents described above). Further, $-NR^{400e}R^{400f}$ may represent heterocyclyl containing =O (for example, 2-pyrrolidinon-1-yl, succinimide, oxazolidin-2-on-3-yl, 2-benzoxazolinon-3-yl, phthalimide, cis-hexahydrophthalimide and the like). T^{401}–T^{404} is the same as R^{401}, which may be optionally substituted with the substituents described above. Q^{400} represents =O or =S.

Compound (IV) exists as either optically active or racemic form due to an asymmetric

carbon atom to which $-(CH_2)_n-Y^{400}$ is bonded. The racemic form can be separated into each of the enantiomers by known techniques. Further, when compound (IV) contains additional asymmetric carbon atoms, it exists as either a single diastereomer or a diastereomeric mixture, which can be separated by known technique.

Compound (IV) may exhibit polymorphism, exist as more than one tautomeric form or exist as solvate (such as ketone solvate and hydrate).

Accordingly, the present invention includes any of stereoisomers, optical isomers, polymorphic forms, tautomeric forms, solvates and any mixtures thereof.

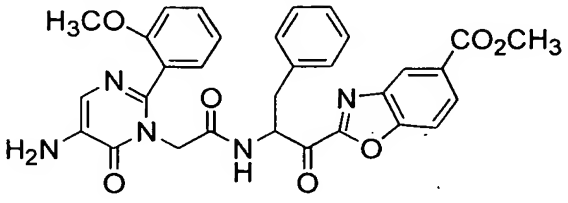
When compound (IV) is acidic, pharmacologically acceptable salts thereof include alkali metal salt (for example, salt with lithium, sodium, potassium or the like), alkaline earth metal salt (for example, salt with calcium, magnesium or the like), aluminum salt, ammonium salt, salt with an organic base (for example, salt with triethylamine, morpholine, piperidine, triethanolamine or the like) and the like.

When compound (IV) is basic, pharmacologically acceptable salts thereof include salt with an inorganic acid (for example, salt with hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid or the like), salt with an organic acid (for example, salt with methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, formic acid, acetic acid, trifluoroacetic acid, oxalic acid, citric acid, malonic acid, fumaric acid, glutaric acid, adipic acid, maleic acid, tartaric acid, succinic acid, mandelic acid, maleic acid or the like), salt with an amino acid (for example, salt with glutamic acid, aspartic acid or the like) and the like.

Suitable examples as compound (IV) include compounds of formula (IV) wherein Y^{400} is aryl optionally having substituents; compounds of formula (IV) wherein Z is the group of formula (IV-i); compounds of formula (IV) wherein one of R^{405}, R^{406} and R^{407} is aryl optionally having substituents with the rest being hydrogen (R^{406} is absent when M^{400} is nitrogen); and the like.

Among the compounds of formula (IV), it was reported that the compound represented by the following formula (IV-I) exhibit activity as a chymase inhibitor in a mouse allergy model and the like through oral administration (WO 00/51640, J. Med. Chem., 2001, vol. 44, p.1286). Therefore it is expected that this compound will be effective as a chymase

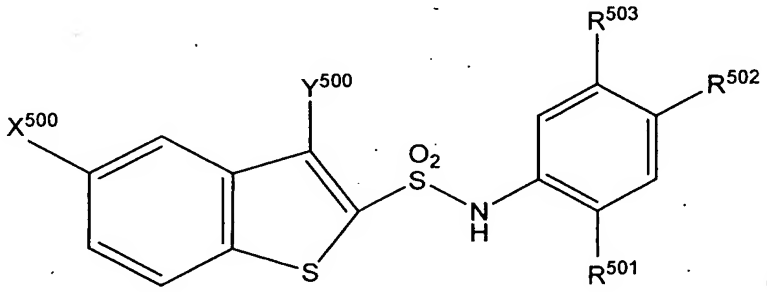
inhibitor in the present invention on various diseases associated with glucose intolerance.



(IV-I)

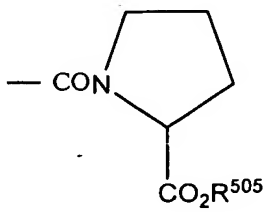
So far, there has been reported a number of chymase inhibitors other than described above. Either of these is potentially valuable for glucose intolerance and various diseases associated with it by using as a chymase inhibitor in the present invention.

An example of such chymase inhibitors is the N-substituted benzothiophenesulfonamide derivative represented by formula (V) or salt thereof described in WO 02/22595:

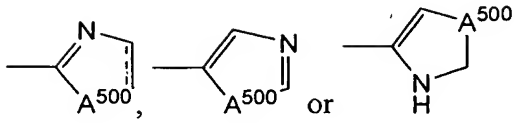


(V)

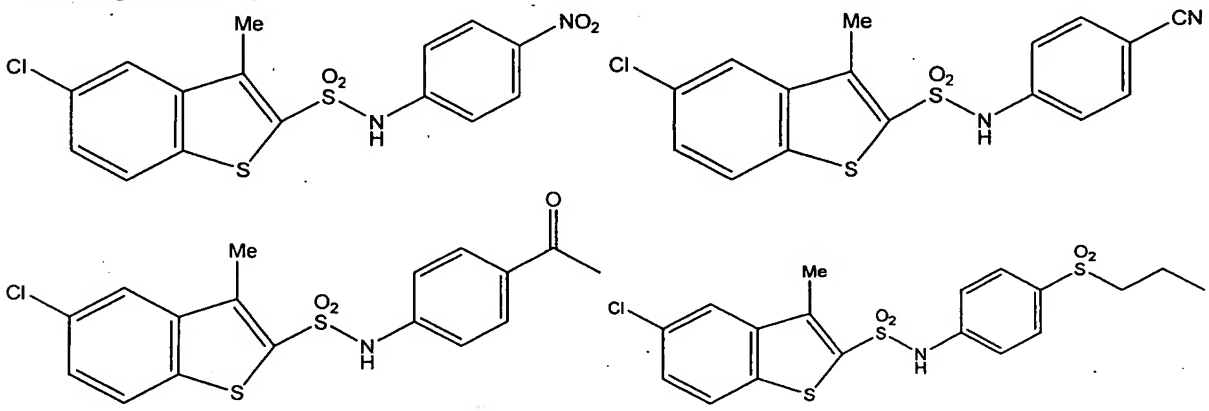
[wherein X^{500} represents hydrogen, halogen or lower alkyl, Y^{500} represents lower alkyl, R^{501} and R^{502} each may be different and represent independently hydrogen, lower alkoxycarbonyl, lower alkylsulfonyl, benzoyl, C_1–C_4 acyl, lower alkoxy, lower alkoxycarbonylmethylthioacetyl, nitro, –$CONHR^{504}$ (wherein R^{504} represents hydrogen, lower alkoxycarbonylmethyl, carboxymethyl or –$CH(CH_2OH)COOR^{505}$ (wherein R^{505} represents hydrogen or lower alkyl)), the group represented by



(wherein R^{505} is as defined above), the monocyclic heterocyclyl represented by



optionally substituted with $-CO_2R^{505}$ (wherein A^{500} represents O, S or NH, the bond accompanying a dotted line represents a single or double bond, and R^{505} is as defined above), lower hydroxyalkyl or cyano (except for cases where both R^{501} and R^{502} are hydrogen), R^{503} represents hydrogen, lower alkoxy or lower alkyl] (except for compounds represented by the following formulas).



Each of the terms in formula (V) is defined as follows:

The halogen as X^{500} is F, Cl, Br or I, preferably F or Cl. The lower alkyl as X^{500} is for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, preferably methyl or ethyl.

The lower alkyl as Y^{500} is for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, preferably methyl or ethyl.

The lower alkoxycarbonyl as R^{501} or R^{502} is for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl or tert-butoxycarbonyl, preferably methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl or tert-butoxycarbonyl.

The lower alkylsulfonyl as R^{501} or R^{502} is for example, methanesulfonyl, ethanesulfonyl, propanesulfonyl, isopropanesulfonyl, butanesulfonyl, isobutanesulfonyl, sec-butanesulfonyl or tert-butanesulfonyl, preferably methanesulfonyl or ethanesulfonyl.

The C_1–C_4 acyl as R^{501}or R^{502} is for example, formyl, acetyl, propionyl, butyryl or isobutyryl, preferably acetyl.

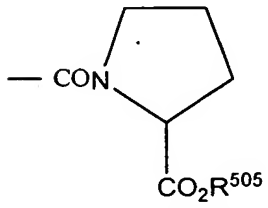
The lower alkoxy as R^{501}, R^{502} or R^{503} is for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy or tert-butoxy, preferably methoxy or ethoxy.

The lower alkoxycarbonylmethylthioacetyl as R^{501} or R^{502} is for example, methoxycarbonylmethylthioacetyl, ethoxycarbonylmethylthioacetyl, propoxycarbonylmethylthioacetyl, isopropoxycarbonylmethylthioacetyl, butoxycarbonylmethylthioacetyl, isobutoxycarbonylmethylthioacetyl, sec-butoxycarbonylmethylthioacetyl or tert-butoxycarbonylmethylthioacetyl, preferably methoxycarbonylmethylthioacetyl or ethoxycarbonylmethylthioacetyl.

When R^{501} or R^{502} is $-CONHR^{504}$, the lower alkoxycarbonylmethyl as R^{504} is for example, methoxycarbonylmethyl, ethoxycarbonylmethyl, propoxycarbonylmethyl, isopropoxycarbonylmethyl, butoxycarbonylmethyl, isobutoxycarbonylmethyl, sec-butoxycarbonylmethyl or tert-butoxycarbonylmethyl, preferably methoxycarbonylmethyl, ethoxycarbonylmethyl or isopropoxycarbonylmethyl.

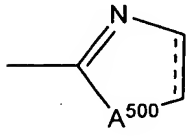
When R^{501} or R^{502} is $-CONHR^{504}$ and R^{504} is $-CH(CH_2OH)COOR^{505}$, the lower alkyl as R^{505} is for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, preferably methyl or ethyl.

When R^{501} or R^{502} is the group represented by



, the lower alkyl as R^{505} is as defined above.

When R^{501} or R^{502} is monocyclic heterocyclyl represented by



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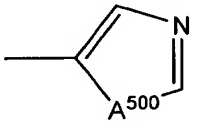
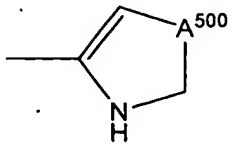
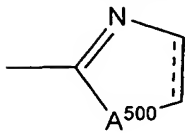


or



(wherein A^{500} represents O, S or NH and the bond accompanying a dotted line represents a single or double bond) which may be optionally substituted with CO_2R^{505}, the lower alkyl as

R^{505} is as defined above. Examples of such monocyclic heterocyclyl represented by



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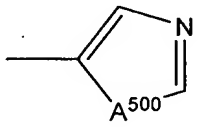
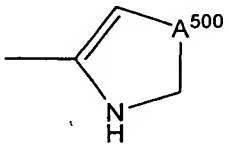


or


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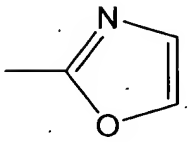

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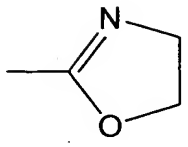

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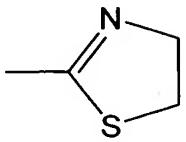

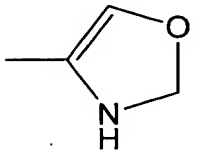

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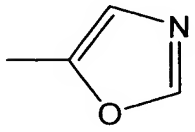

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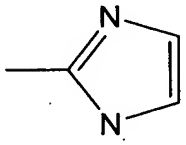

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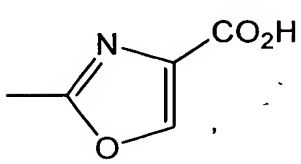
Specifically, preferred groups are



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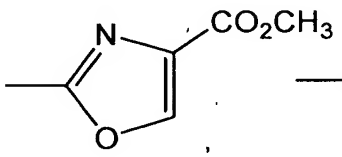

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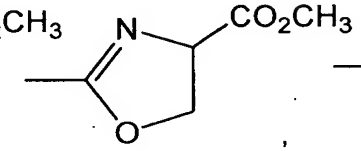

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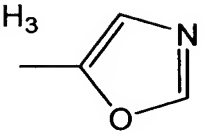

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These substituents are preferably present as R^{502}. In this case, further preferably R^{501} is methanesulfonyl and R^{503} is hydrogen.

The lower hydroxyalkyl as R^{501} or R^{502} is straight or branched lower hydroxy(C_1–C_4)alkyl, for example, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl or the like, preferably hydroxymethyl, 1-hydroxyethyl or 2-hydroxyethyl.

The lower alkyl as R^{503} is for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, preferably methyl or ethyl.

Examples of the compound (V) are specifically methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, sodium 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, isopropyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, N-(4-acetyl-2-methanesulfonylphenyl)-5-chloro-3-methylbenzo[b]thiophene-2-sulfonamide,

N-(4-benzoyl-2-methanesulfonylphenyl)-5-chloro-3-methylbenzo[b]thiophene-2-sulfonamide, ethyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, tert-butyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-ethanesulfonylbenzoate, methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-5-methanesulfonyl-2 -methylbenzoate, dimethyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)isophthalate, methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methoxybenzoate, methyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-nitrobenzoate, ethyl 4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)benzoate, N-[2,4-bis(methanesulfonyl)phenyl]-5-chloro-3-methylbenzo[b]thiophene-2-sulfonamide, N-(4-acetyl-2-nitrophenyl)-5-chloro-3-methylbenzo[b]thiophene-2-sulfonamide, N-(4-hydroxymethyl-2-methanesulfonylphenyl)-5-chloro-3-methylbenzo[b]thiophene-2 -sulfonamide, N-(4-benzoylphenyl)-5-chloro-3-methylbenzo[b]thiophene-2-sulfoamide, N-(2-methanesulfonylphenyl)-5-chloro-3-methylbenzo[b]thiophene-2-sulfonamide, methyl 4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, methyl 4-(5-methyl-3-methylbenzo[b]thiophene-2-sulfonylamino) -3-methanesulfonylbenzoate, N-(4-acetyl-2-methanesulfonylphenyl)-5-fluoro-3-methylbenzo[b]thiophene-2-sulfonamide, methyl 4-(3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylbenzoate, methyl 2-[4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl] oxazole-4-carboxylate, methyl 2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl] oxazole-4-carboxylate, 2-[4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl] oxazole-4-carboxylic acid, 2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl] oxazole-4-carboxylic acid, sodium

2-[4-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl] oxazole-4-carboxylate, sodium
2-[4-(5-fluoro-3-methylbenzo[b]thiophene-2-sulfonylamino)-3-methanesulfonylphenyl] oxazole-4-carboxylate and
2-[4-(5-fluoro-3-methylbenzo[b]thiophen-2-yl)sulfonamido-3-methanesulfonylphenyl] oxazole-4-carboxylic acid.

The chymase inhibitor also includes
4-[1-{[bis(4-methylphenyl)methyl]carbamoyl}-3-(2-ethoxybenzyl)-4-oxoazetidin-2-yloxy] benzoic acid and
2-(5-formylamino-6-oxo-2-phenyl-1,6-dihydropyrimidin-1-yl)-N-[{3,4-dioxo-1-phenyl-7-(2-pyridyloxy)}-2-heptyl]acetamide.

Other chymase inhibitors proposed so far include for example, compounds described in WO 01/32214, WO 02/18378, WO 01/12226, WO 01/32621, Japanese published unexamined application H10-87493, Japanese published unexamined application H11-1479, Japanese published unexamined application H10-251239, Japanese published unexamined application H8-208654, Japanese published unexamined application 2001-97957 and Japanese published unexamined application 2000-95770.

Any compound that inhibits human chymase activity may be used as a chymase inhibitor in the present invention. Specifically, it is the chymase inhibitor with an IC_{50} value, determined by method (A) for IC_{50} assay described below, of preferably 1000 nM or less, more preferably 500 nM or less, further preferably 100 nM or less, still further preferably 10 nM or less.

The method (A) for IC_{50} assay is as follows. First, recombinant human mast cell prochymase is prepared according to the report of Urata et al. (J. Biol. Chem., vol. 266, p. 17173 (1991)). Namely, prochymase is purified from supernatant of a culture medium of insect cells (Tn5) infected with recombinant baculoviruses containing cDNA coding human mast cell chymase, by heparin-sepharose. After activation of the prochymase according to the report of Murakami et al. (J. Biol. Chem., vol. 270, p. 2218 (1995)), purification on heparin-sepharose column gives active form of human mast cell chymase. Next, the inhibitory

activity against recombinant human mast cell chymase is assayed. To 50 μL of buffer A (0.5–3.0 M NaCl, 50 mM Tris-HCl, pH 8.0) containing 1–5 ng of active form of human mast cell chymase prepared above, are added 2 μL of DMSO solution containing a chymase inhibitor and then 50 μL of buffer A containing 0.5 mM succinyl-alanyl-histidyl-prolyl-phenylalanyl-p-nitroanilide as a substrate. The resultant mixture is kept at room temperature for 5 min to allow the reaction to occur. The time course of absorbance at 405 nm is monitored to determine the inhibitory activity. This method is the same as that described in Examples 16 and 17 in WO 01/53291.

Other methods for IC_{50} assay are described in Examples 19 and 20 in WO 01/53272, Examples 22 and 23 in WO 00/03997, Test example 1 in WO 00/005204, Test example 1 in WO 98/009949 and Experimental example 1 in WO 98/018794. In each of these reports it was confirmed that the compound described therein exhibits inhibitory activity against chymase by using the method described therein.

Furthermore, the drugs for improving glucose intolerance containing chymase inhibitors of the present invention as active ingredients can be used together with other drugs for improving glucose intolerance, improving insulin resistance or treating diabetes and/or diabetes complications, and in some cases synergistic effects may be expected by combination. Drugs that may be used together include PPARγ agonists such as rosiglitazone and pioglitazone, which improve glucose intolerance, and the like.

Also, it was reported that AT1 receptor antagonists which suppress major functions of angiotensin II irrespective of production pathways of angiotensin II, being ACE-dependent or ACE-independent, exhibit activity for improving insulin resistance (Effects of angiotensin receptor antagonist and angiotensin converting enzyme inhibitor on insulin sensitivity in fructose-fed hypertensive rats and essential hypertensives, American Journal of Hypertension, USA, 1995, vol. 8, part 4, No. 1, p. 353), that ACE inhibitors for treating hypertension such as captopril (CARPPP clinical study) and ramipril (HOPE study) or losartan which is an AT1 receptor antagonist (LIFE study) suppress new onset of diabetes in large scale clinical tests (Cardiovascular morbidity and mortality in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol, Lancet, USA, 2002, vol. 359,

no. 9311, p. 995), and that imidapril which is an ACE inhibitor has been indicated for diabetic nephropathy associated with type I diabetes. Accordingly, it is preferred to use these drugs such as ACE inhibitors together with the drugs of the present invention.

The drug of the present invention may be in any dosage form as long as it contains a chymase inhibitor as an active ingredient.

Possible dosage forms include tablets, pills, granules, powder, liquid, suspension, syrup, capsules and the like. The dosage form is not particularly limited and may be a solid-solid, liquid-liquid or solid-liquid mixture. The drug may be administrated orally or parenterally.

Among the chymase inhibitors in the present invention, benzimidazole derivatives represented by formula (I) are preferably administrated orally or parenterally as medicinal compositions with pharmaceutically acceptable carriers in various dosage forms.

Possible dosage forms for the medicinal compositions in the present invention include, in the case of oral administration, tablets, pills, granules, powder, liquid, suspension, syrups, capsules and the like.

Here tablets can be shaped with pharmaceutically acceptable carriers such as excipients, binders and/or disintegrants by usual methods. Pills, granules and powder can similarly be formed by usual methods with excipients and the like. Liquid, suspension and syrups can be formed by usual methods with glycerol esters, alcohols, water and/or vegetable oils. Capsules can be formed by filling capsules such as gelatin with granules, powder or liquid.

EXAMPLES

The present invention will be explained by an example bellow, which should not be construed to limit the scope of the present invention in any sense.

[EXAMPLE 1]

Improving activity for glucose intolerance

A group of 22 weeks-old wild type mice (C57Black) (Wild), a group of those in which human chymase gene was expressed (TGM) and a group of TGM that had been given feed

containing 0.1% sulfate of compound 58 (the IC_{50} value of compound 58 is between 1 nM and 10 nM) as a chymase inhibitor (ChI) continuously for 12 weeks since 10 weeks old (TGM/ChI) were made fast overnight and orally administrated with 1.5 g/kg glucose. At 60 min after glucose load the concentrations of glucose and insulin in blood were assayed.

Results:

At 60 min after glucose load, the blood glucose levels were 119±20 mg/dl for Wild, 181±22 mg/dl for TGM and 134±18 mg/dl* for TGM/ChI (mean±SD, *$p<0.01$ vs. Wild, $p=0.01$ vs. TGM), indicating that the blood glucose level after glucose load significantly increased in TGM and that administration of ChI significantly repressed the increase (Fig.1).

On the other hand, the insulin concentrations in blood at this time were 386±97 ng/l for Wild, 809±288 ng/l for TGM and 425±158 ng/l for TGM/ChI (mean±SD), indicating that it significantly increased in TGM and that administration of ChI significantly repressed this increase, as in the case of the blood glucose level (Fig. 2).

It has been found that, compared with the wild type mice, mice in which human chymase gene is expressed exhibit significantly high values of the blood glucose level and the blood insulin concentration, showing that the glucose intolerance is caused by the expression of human chymase. It has also been shown that administration of a chymase inhibitor remarkably reduces the blood glucose level and the blood insulin concentration, improving glucose intolerance. Accordingly, it is clear that chymase inhibitors used in the present invention are inhibitors against human chymase that can be clinically applicable to inhibiting and/or treating various diseases associated with glucose intolerance induced by human chymase.

INDUSTRIAL APPLICABILITY

The drugs comprising chymase inhibitors in the present invention can be used for improving glucose intolerance or for preventing and/or treating diabetes and/or diabetes complications such as diabetic nephropathy, diabetic retinopathy, diabetic peripheral neuropathy, hyperinsulinism, insulin resistance syndrome, arteriosclerosis, acute coronary syndrome, arteriosclerosis obliterans, angitis, stroke, hypertension, renal insufficiency, nephropathy, nephritis, renal artery aneurysm, renal infarction, obesity and the like.